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Review article

Altered cytokine levels and immune responses in patients with SARS-CoV-2 infection and related conditions

Rezvan Noroozi[a], Wojciech Branicki[a], Krzysztof Pyrc[a], Paweł P. Łabaj[a], Ewelina Pospiech[a], Mohammad Taheri[b,*], Soudeh Ghafouri-Fard[c,*]

[a] Malopolska Centre of Biotechnology, Jagiellonian University, Kraków, Poland
[b] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic in early 2020. The infection has been associated with a wide range of clinical symptoms. In the severely affected patients, it has caused dysregulation of immune responses including over-secretion of inflammatory cytokines and imbalances in the proportion of naïve helper T cells, memory helper T cells and regulatory T cells. Identification of the underlying mechanism of such aberrant function of immune system would help in the prediction of disease course and selection of susceptible patients for more intensive cares. In the current review, we summarize the results of studies which reported alterations in cytokine levels and immune cell functions in patients affected with SARS-CoV-2 and related viruses.

1. Introduction

Firstly, identified in an outbreak in Wuhan city of China, the novel coronavirus disease 2019 (COVID-19) has caused a global pandemic in early 2020. Alternatively named as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus has been shown to induce various clinical manifestation in hosts ranging from asymptomatic conditions to severe symptoms including respiratory failure, shock, or multiorgan system dysfunction [1]. Identification of IgM and IgG antibodies in the affected persons implies the development of immunity against SARS-CoV-2 [2–4]. However, the virus might also induce dysregulation of immune responses in susceptible individuals as demonstrated by the decreased lymphocytes counts especially T cells, increased leukocytes counts and neutrophil–lymphocyte-ratio and other imbalances in the population of immune cells. Moreover, severely affected patients have shown raised concentrations of infection-related markers and over-secretion of inflammatory cytokines. Notably, this condition has been accompanied by a significant increase in the proportion of naïve helper T cells while reduction in memory helper T cells and regulatory T cells [5]. Based on the importance of immune responses in the determination of course of infection and the related complications, we performed a literature search to find the reported dysregulations in the levels of cytokines and immune cells in patients infected with SARS-CoV-19 and related viruses.

2. SARS-CoV-2

A recent study in Chinese patients affected with SARS-CoV-2 has shown elevated plasma concentrations of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFN-γ, IFN-γ-induced protein (IP)-10, monocyte chemotactic protein 1 (MCP1), MIP1A, MIP1B and TNF-α in both patients needed ICU admission and non-ICU patients compared with healthy controls at initial assessment. Notably, author reported significant over-production of IL-2, IL-7, IL-10, GCSF, IP-10, MCP1, MIP1A, and TNF-α in ICU patients compared with other group of SARS-CoV-2 infected persons [6]. Another study has demonstrated associations between severity of SARS-CoV-2 infection and levels of IL-2R, IL-6, IL-8, IL-10 and TNF-α. Moreover, disease severity was associated with both WBC and lymphocyte counts as well as quantities of neutrophils and eosinophils. Authors have suggested the IL-2R level > 793.5U/mL, WBC > 9.5*10^9/L or neutrophil count > 7.305*10^9/L among parameters that indicate progression of SARS-CoV-19 infection to critical conditions. Thus, inflammatory responses were shown to be correlated with the severity of SARS-CoV-19. Besides, IL-6, TNF-α and IL-8 have been suggested as therapeutic targets [7]. A longitudinal study of cytokine levels and lymphocyte count in affected patients has

* Corresponding authors.
E-mail addresses: mohammad_823@yahoo.com (M. Taheri), s.ghafourifard@sbmu.ac.ir (S. Ghafouri-Fard).

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revealed remarkable and continuous decreases in lymphocyte counts but elevations in neutrophil counts in severely infected cases compared with mild cases. Additionally, severely affected individuals had substantial reductions in T cells population, particularly CD8 + T cells, and upsurge in IL-6, IL-10, IL-2 and IFN-γ levels. Notably, T cell counts and cytokine concentrations in severe SARS-CoV-2 infected patients who stayed alive gradually returned to their levels in the mild cases. The most significant prognostic marker to show the course of infection has been the neutrophil-to-CD8 + T cell ratio [8]. IL-6 has also been among the up-regulated infection-related markers in the serum of patients with SARS-CoV-2 pneumonia [9]. Another study has demonstrated significant decrease in lymphocyte subsets both in severe and mild groups of patients with SARS-CoV-2 infection. Reduction in CD8 + T cells and increase in IL-6 levels were more prominent in the severely affected patients. Moreover, significant differences were detected between the severe and mild groups in CD4 + T, CD8 + T, IL-6 and IL-10 [7].

3. SARS-CoV

Cellular immune responses to SARS-CoV infection have been previously assessed in an animal study. Animals were exposed to the virus through an intranasal route. Such viral administration resulted in induction of pneumonia which was accompanied by over-production of TNF-α, IL-6, CXCL10, CCL2, CCL3, and CCL5. Notably, increased cytokine and chemokine levels were associated with relocation of NK cells, macrophages, and plasmacytoid dendritic cells (pDC) into the lungs. The viral clearance was accompanied by another round of cytokine and chemokine release and an inflow of T lymphocytes occurred. Depletion studies showed the essential role of CD4 + but not CD8 + T cells in reduction of immune-mediated interstitial pneumonitis and enhancement of elimination of SARS-CoV from the lungs [10]. An in vitro study has shown insignificant induction of IFN-β expression in SARS-CoV infected macrophages, while up-regulation of CXCL10/IFN-γ-inducible protein 10 and CCL2/monocyte chemotactic protein 1 [11]. Wong et al. have assessed a number of cytokines and chemokines in patients affected with SARS. They detected significant increase in Th1 cytokine IFN-γ, inflammatory cytokines IL-1, IL-6 and IL-12, and some chemokines such as IL-8, MCP-1 and IP-10. Levels of chemokines were significantly decreased after corticosteroid therapy. They concluded induction of Th1 cell-mediated immune response in patients. This observation was associated with induction of monocytes/macrophages and neutrophils [12]. In another study in the pediatric setting, Ng et al. have demonstrated significant increase in circulating IL-1β concentrations. Yet, IL-6 and TNF-α cytokines were slightly increased at the primary phase of the disease [13]. Zhang et al. did not detect any significant difference IL-1 and TNF-α levels between normal controls, patients with SARS, severe SARS or those with SARS in convalescence. IL-6 levels were higher in SARS particularly those with severe SARS course. Yet, IL-6 levels were not different between convalescent patients and healthy control, indicating the presence of a positive correlation between the serum IL-6 levels and severity of the disorder. On the other hand, IL-8 and TGF-β levels were negatively correlated with SARS severity. IFN-γ and IL-4 concentrations were reduced, whereas IL-10 concentrations were elevated in convalescent SARS patients. Taken together, various immunoregulatory conditions are present during and subsequent to SARS infection [14].

4. Middle east respiratory syndrome coronavirus (MERS-CoV)

Lau et al. have assessed transcript levels of TNF-α, IL-1β, IL-6, IL-8, IFN-β, MCP1, TGF-β and IP-10 in cell lysates of polarized airway epithelial Calu-3 cells infected with MERS-CoV or SARS-CoV. MERS-CoV induced higher levels of IL-1β, IL-6 and IL-8, while lower levels of TNF-α, IFN-β and IP-10 compared with SARS-CoV. Their experiments confirmed the diminished induction of innate immunity and postponed proinflammatory cytokine production by MERS-CoV [15]. Kim et al. have reported higher neutrophil counts in severe MERS-CoV compared with mild cases. Moreover, IL-6 and CXCL-10 levels were higher in severe cases compared with mild cases. Besides, they could not detect IFN-α response in mild cases [16]. Zhou et al. have shown ability of MERS-CoV but not SARS-CoV in replication in monocyte-derived macrophages. MERS-CoV induced remarkably elevated concentrations of IL-12, IFN-γ, and chemokines compared with SARS-CoV [17]. Mahallawi et al. have demonstrated a noticeable pro-inflammatory Th1 and Th17 response in patients affected with MERS-CoV. These patients had elevated levels of IFN-γ, TNF-α, IL-15 and IL-17 compared to controls. Totally, cytokines profiles indicated an obvious pro-inflammatory immune reactions in the acute course of MERS-CoV infection [18].

5. Influenza

Pirhonen et al. have demonstrated induction of trivial amounts of IL-1β or IL-18 in influenza virus-infected monocytes, while GM-CSF-differentiated macrophages secreted high amounts of these cytokines. In vitro experiments indicated that the role of cellular differentiation in the aptitude of monocytes/macrophages to secrete IL-1β and IL-18 following exposure with virus infections [19]. In addition, Ramos et al. have reported lower monocyte counts and a marginally lower median level of IL-6 in patients infected with influenza compared with the control group [20].

Table 1 summarizes the results of studies which reported altered cytokine levels and immune functions in patients with SARS-CoVs and influenza infections and related conditions.

6. Discussion

Immune responses have indispensable functions in the determination of course of SARS-CoV infection. Dysregulation of cytokine levels have been demonstrated in almost all patients with this infection. Moreover, evident differences have been reported in the levels of several cytokines between severely affected patients and those with moderate or mild symptoms [6]. Identification of these aberrant reactions not only helps in recognition of patients who are predisposed to severe complications, but also would specify those would benefit from immune-modulating therapies. Due to the insufficiency of data on SARS-CoV-2, assessment of immune responses in other related disorders would provide a scheme permitting the anticipation of immune-related events which occur in the course of this novel infection. Yet, any of these viruses might exert some specific effects in the host. This speculation has been supported by an in vitro study on expression signatures of macrophages infected with SARS-CoV, human coronavirus 229E, and influenza A (H1N1) virus. Authors have reported slight or no induction of IFN-β in SARS-CoV-infected macrophages. Yet, expression of this cytokine was induced in the macrophages infected with human coronavirus 229E and influenza A virus [11]. Moreover, there were significant differences in the pattern of cytokine induction between SARS-CoV and MERS-CoV [15]. It is worth mentioning that although low-level of SARS-CoV productive infection has been demonstrated in human monocytes/macrophages, these viruses have been identified in phagolysosomes but not on the cell surface implying absence of specific receptors for SARS entrance on macrophages [34]. Low efficiency of macrophage infections by this virus and production of IFN-α by these cells might be involved in the restriction of the infection in human subjects [34]. Similarly, SARS-CoV-2 cannot replicate in macrophages possibly due to lack of ACE2 expression (https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2). Banerjee et al. have assessed an extensive spectrum of human immune cells for productive infection with this virus and verified lack of permissivity of human primary peripheral blood mononuclear cells to this virus [35].

Others have shown infection of human macrophages by SARS-CoV via an IgG-mediated antibody-dependent enhancement mechanism

Table 1
Summary of studies which reported altered cytokine levels and immune functions in patients with SARS-CoV infections and related conditions.

Disease	Case/Control	Sample	Finding Cytokines	Immune cells	Comment	Ref
SARS-CoV-2	40 cases:13 Severe, 27 mild	Blood	Elevated IL-6, IL-10, IL-2, IFN-γ levels in severe cases	Increased neutrophil, decreased lymphocyte counts esp. CD8 + T in severe cases	N8R ratio as a as a prognostic factor	[8]
	99 cases	Blood	Increased IL-6	Increased leucocytes, neutrophils, decreased lymphocytes	–	[9]
	41 cases: 13 ICU/ 28 non-ICU patients	Plasma	Elevated IL-10, IL-2, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα in ICU patients	–	–	[3]
	100 cases: 34 mild, 34 severe, 32 critical	Blood	A significant association between IL and 6, IL-10, IL2R, IL-8, TNFα, CRP, ferroprotein, procalcitonin, and disease severity	A significant association between WBC, lymphocyte, neutrophil and eosinophil counts and disease severity	IL-6, TNFα, IL-8 as promising therapeutic targets	[7]
	53 cases:34 severe, 19 mild	Plasma	Association of IP-10, MCP-3, IL-1ra with disease severity	–	–	[6]
	123 cases:21 severe, 102 mild	Blood	Elevated IL-6 and IL-10 in severe NCP	Decreased CD4 + T, CD8 + T in severe NCP	T cell subsets and cytokines as predictive factors for severity.	[7]
MERS	Case report of a child with influenza associated MERS	CSF and serum	Elevated IL-10 and IFN-γ in early phase in CSF	–	–	[21]
	MERS infected cells/SARS infected cells	Calu-3 cells	Higher IL-1β, IL-6 and IL-8 induced by MERS, higher TNF-α, IFN-β and IP-10 induced by SARS-CoV	–	Delayed proinflammatory cytokine induction by MERS-CoV	[15]
	MERS-infected MDMs/SARS infected MDMs	MDM cells	Elevated TNF-α, Il-10 in both cells, higher MERS induced IL-8, IL-12, IFN-γ, IP-10/CXCL-10, MCP1/CCL-2, MIP-1α/CCL-3, RANTES/CCL-5	–	None of the viruses were able to induce IFN-α and IFN- β.	[17]
	17 cases	Serum	Elevated IL-6 and CXCL-10	–	Elevated serum levels of IL-6 and CXCL-10 in severe patients	[16]
	7/13	Plasma	Elevated IFN-γ, TNF-α, Il-10, IL-15 and IL-17	–	MERS induced Th1 and Th17 cytokine profile	[18]
	14 cases: 4 groups based on severity	Plasma	Elevated IFN-α, G-CSF, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-15, IL-17A, IFN-γ, TGF-β, MCP-1 (CCL2), IP-10 (CXCL10), MDC (CCL22), RANTES (CCL5), IL-8 (CXCL8), MIP-1 (CCL3), Eotaxin (CCL11), and GRO (CXCL1)	Increased lymphocytes, neutrophils, leukocytes and monocytescounts	IL-10, IL-15, TGF-β, and EGF were correlated with disease severity	[22]
SARS	8 children before corticosteroids therapy/after 1–2 days/after 7–10 days	Plasma	Elevated IL-1β -before and 7–10 days after therapy,decreased IL-10, IL-6, IL-8	–	TNF-α was not significantly elevated thus TNF-α monoclonal antibody was not recommended.	[13]
	SARS infected cells / cells infected with RSV, FluAV, and hPIV2.	Caco2 cells	Induced high levels of IL-6, IFN-β, TLR4, TLR9	–	–	[23]
	88 cases 51 Ab positive/37 Ab negative	Serum	Elevated IFN- γ, IL-18, TGF- β, IL-6, IP-10, MCP-1, MIG, and IL-8	–	IFN- γ induced cytokine storm after viral infection	[24]
	20 cases	Plasma	Elevated IL-1, IL-6, IL-8,IL-12, IFN-γ, MCP-1, IP-10	Accumulation of monocytes/macrophages and neutrophils	Th1 cell-mediated immunity and hyperinnate inflammatory response in SARS.	[12]
	228 cases	Serum	Elevated IL-6, decreased IL-8 and TGF-β	–	Elevated IFN-γ, IL-4 and decreased IL-10 only in convalescent SARS patients.	[14]
	61 cases:initial stage, peak stage, remission,recovery stage / 44 Healthy control	Serum	Elevated IL-6, IL-8, TNF-α, IL-16, TGF-β1, decreased IL-18	–	The mean concentration of IL-13 gradually decreased from initial stage to recovery.	[25]

(*continued on next page*)

Table 1 (*continued*)

Disease	Case/Control	Sample	Finding Cytokines	Immune cells	Comment	Ref
Influenza	–	HMC	IL-1β mRNA expression was induced by influenza A and Sendai viruses.	–	Virus induced IL-1β and IL-18 expression and activation is related to cellular differentiation and caspase-1-dependent pathway.	[19]
	19 cases	Nasal lavage fluid, plasma, serum	Elevated IL-6, IL-8, IFN-α	–	–	[26]
	–	Human primary alveolar and bronchial epithelial cells	IP-10, IFN-β, RANTES, IL-6	–	–	[27]
	77/17	Nasal lavage fluid	Lower IL-6	Lower monocyte counts	Pro-inflammatory cytokines levels were not elevated in patients with pneumonia.	[20]
ARDS	51 casesat the time of ECMO installation/ 6 h later	Plasma	Elevated IL-10 and IL-8 levels	Higher Treg, CD14 + CD16+, CD14 + TLR4 + cell counts in survivors	IL-10 levels predict ICU mortality.	[28]
	300/300	Plasma	Higher TNF-α, IL-6 levels in patients	–	Functional polymorphisms in TNF-α, IL-6, MyD88 are associated with ARDS mortality.	[29]
Pneumonia	15 severe/15 non-severe CAP	Blood	Elevated IL-6, IL-10, IL-8, CRP levels	–	IL-6 sharp decrease was associated with response to empirical antibacterial treatment by day 3.	[30]
Septic shock	Endotoxin-stimulated septic monocytes/normal monocytes	Serum	Elevated IL-10, attenuated TNF-α in septic serum	–	The persistent release of IL-10 leads to impaired proinflammatory cytokine release and the immune dysfunction in septic shock.	[31]
	16 septic shock/ 11 circulatory shock	Plasma	More increased IL-10 in septic shock cases	–	The production of the IL-10 positively correlates with the intensity of the inflammatory response in septic shock.	[32]
Febrile illness	464 cases431 survived/ 33 dead	Plasma	Higher IL-10 and lower TNFα in patients who died	–	IL-10 to TNFα ratio was associated with mortality of CAI.	[33]

Severe acute respiratory syndrome coronavirus 2, Neutrophil-to-CD8 + T cell ratio (N8R), 2019 novel coronavirus pneumonia (NCP), Human Macrophage Cell (HMC), human monocyte–derived macrophages (MDMs), human monocyte-derived dendritic cells (DCs), SARS sera antibody (Ab positive), cerebrospinal fluid (CSF), Acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO), community-acquired pneumonia (CAP), community-acquired infection (CAI).

[36]. The significant increase in plasma IL-1β concentrations in SARS patients have also implied the presence of a selective caspase-1-dependent route in induction of macrophages that are infected with this virus [13].

Animal studies have previously highlighted the role of CD4 + T cells in the inhibition of immune-mediated interstitial pneumonitis, enhancement of SARS-CoV elimination from the lungs, production of neutralizing antibody and cytokines and recruitment of lymphocytes to the lung [10]. However, there is no comprehensive data about the role of these cells in the course of SARS-CoV-2 infection. Yet, as noted by most of studies, the level of lymphopenia and upsurge of proinflammatory cytokines are determinants of severe SARS-CoV-2 infection [8]. Lymphopenia in severe cases include both CD4 + T and CD8 + T subsets [7]. Meanwhile, elevated levels of IL-6 and IL-10 has been suggested as factors that predict severe course of the disorder [7].

Taken together, the data presented above show some levels of similarity in the levels of proinflammatory cytokines particularly IL-6 and IL-10 as well as T cell subsets among different coronaviruses which indicate the role of these cytokines in the pathogenesis of infection-related complications. Future studies are needed to find the practical modalities to defend these aberrant responses and improve the clinical outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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