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REVIEW

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Dysregulation of the immune response in coronavirus disease 2019

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger a cytokine storm in the pulmonary tissue by releasing various types of mediators, leading to acute respiratory distress syndrome (ARDS). Increased neutrophil-to-lymphocyte ratio, as well as CD4+ T lymphopenia, is reported in cases with novel coronavirus disease (COVID-19), meanwhile, lymphopenia is a significant finding in the majority of COVID-19 cases with a severe phenotype. Moreover, excessive activation of monocyte/macrophage and cytokine storms are associated with the severity of the disease and the related complications in SARS-CoV-2 infection. Understanding the immune response dysregulation in COVID-19 is essential to develop more effective diagnostic, therapeutic, and prophylactic strategies in this pandemic.

KEYWORDS

acute respiratory distress syndrome, coronavirus disease, cytokine storm, immune dysregulation, lymphopenia, severe acute respiratory syndrome coronavirus

1 | INTRODUCTION

The first patients with pneumonia of an unknown origin were reported in early December 2019 in Wuhan, Hubei province, China. The cause of pneumonia in these cases was a novel beta coronavirus (β CoV) with enveloped RNA that was previously called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to the similar phylogenetic with SARS-CoV (Golshani et al., 2020; Lotfi & Rezaei, 2020). The World Health Organization (WHO) has stated that coronavirus disease 2019 (COVID-19) is a public health emergency of pandemic proportions (Guan et al., 2020). In addition to a huge burden on public health with a high rate of mortality, this pandemic has already distinctly affected the global economy and civil societies (Hanaei & Rezaei, 2020; Jabbari et al., 2020; Momtazmanesh et al., 2020). The risk of the severe form of the disease is more likely in patients with underlying conditions such as hypertension, cardiovascular disease, and diabetes mellitus (Huang et al., 2020; Qin et al., 2020). The virus can trigger a terrible cytokine storm in the pulmonary tissue by releasing various types of mediators causing edema, air exchange dysfunction and acute respiratory distress syndrome (ARDS), acute cardiac injury followed by a secondary infection which may lead to death (Huang et al., 2020; A. Saghazadeh & N. Rezaei, 2020; Xu et al., 2020). Several studies highlight relevant dysregulation both in innate and adaptive immune systems in COVID-19 patients (Qin et al., 2020). Dysregulation of the immune response influences the outcome in critical COVID-19 patients. For the development of drugs and vaccines during the epidemic and pandemic outbreak of a new virus, understanding the immune responses against the virus is essential (Lotfi, Hamblin, & Rezaei, 2020; Mansourabadi et al., 2020).

2 | DYSREGULATED IMMUNITY IN COVID-19

In a cohort study in Wuhan, China, the dysregulated immune system has been confirmed in 452 patients with laboratory-confirmed COVID-19. The increased neutrophil-to-lymphocyte ratio (NLR) as

Abbreviation: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; β CoV, beta coronavirus; COVID-19, coronavirus disease; FABP4, fatty acid-binding protein-4; ICU, intensive care unit; MASP-2, mannose associated serine protease 2; NLR, neutrophil-to-lymphocyte ratio; NK, natural killer; NKG2A, NK group 2 member A; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

well as T lymphopenia, especially decreased number of $CD4^+$ T cells, was typical in COVID-19 patients, particularly among the severe cases. However, no significant alteration in the $CD8^+$ cells and B cells was reported, suggesting the lymphocytes impairment, especially T cells immune system dysfunction during the period of illness in COVID-19 (Qin et al., 2020; Wei et al., 2020). NLR, which is a well-known factor to show systemic infection and inflammation, has been studied as a predictor of bacterial infection including pneumonia (Berhane et al., 2019; X. Liu et al., 2016). An increased number of neutrophil and a decreased number of lymphocyte were reported in several patients with COVID-19 during the severe phase, indicating a serious disturbance in the internal environment and potential critical condition in those severe infected cases (Fathi & Rezaei, 2020; J. Liu, Wan, et al., 2020).

The gravity of a viral disease can be determined by direct cytopathic effects exerted by the virus as well as the circumvention of host immune responses (Channappanavar & Perlman, 2017; Min et al., 2016). A rapid and well-coordinated innate immune response is believed to play a critical role as the first line of defense against viral infections; however, dysregulation of the immune response leads to exacerbated inflammatory responses, even resulting in death (Shaw et al., 2013). Increased loss of dendritic cell (DC) function could result in delayed T cell responses in COVID-19 patients. DCs play a substantial role in the interaction between innate and adaptive immunity. Plasmacytoid dendritic cell (pDC) is the main potent IFN-I producer against viral infection. Accordingly, the substantial loss of pDC together with a decrease in NK cell could lead to instant destruction of innate immunity against SARS-CoV-2 infection (Chu et al., 2020; R. Zhou et al., 2020).

Massive upregulation of proinflammatory cytokines and chemokines and $CD4^+$ and $CD8^+$ T cells consumption, as well as reduced regulatory T cells in patients with COVID-19, mainly in the severe illness, may contribute to exacerbated inflammatory responses, the cytokine storm induction, and ultimately aggravated lung injury (Grifoni et al., 2020). However, correlative evidence from those severe patients with a lower number of lymphocytes reveals the role of dysregulated immune responses in the pathogenesis of COVID-19 (J. Chen et al., 2010; Qin et al., 2020; Rokni et al., 2020). So, SARS-CoV-2 infection might majorly affect the lymphocytes, especially T cells, and induce a cytokine storm in the body, resulting in several immune responses to impair the corresponding organs. NLR can be served as an independent prognostic marker of disease severity in COVID-19 (Rokni et al., 2020). In addition, lymphopenia and enhanced NLR are highly correlated with COVID-19 disease severity/outcome. Therefore, surveillance of NLR and lymphocyte subsets is a useful marker in the early screening of patients and is a specific strategy to diagnose and treat COVID-19 patients (J. Liu, Li, et al., 2020; Qin et al., 2020; A. Saghazadeh & N. Rezaei, 2020; Figure 1).

3 | DYSREGULATION OF MONOCYTE/MACROPHAGE IN SARS-COV-2

Lymphopenia is as commonplace as the hematologic abnormality in up to 85% of patients with severe COVID-19 (Qin et al., 2020). Regulatory T cells have been shown to play an essential role in

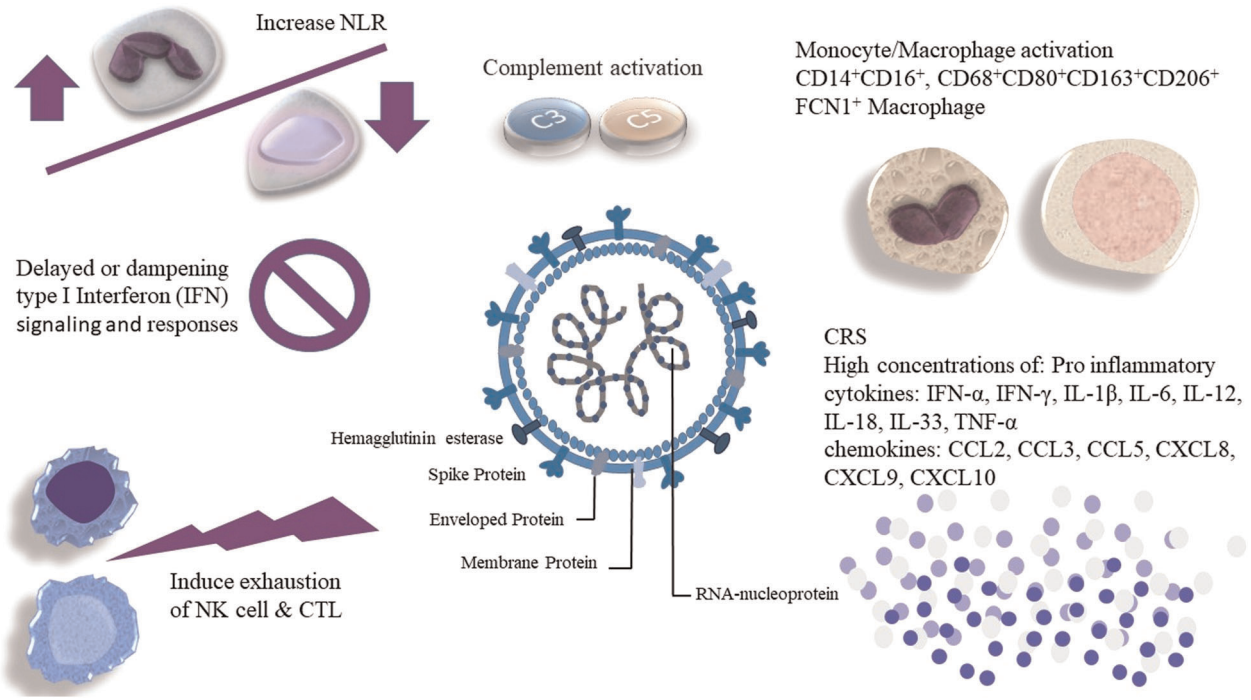

FIGURE 1 Dysfunctional and dysregulation of innate and adaptive immune responses. Uncontrolled monocyte-macrophage activation, complement hyper-activation, and inflammatory responses resulting in tissue damage and systemic inflammation; both contribute to morbidity and mortality in patients with coronavirus disease 2019

weakening the immune response. Thus, a massive reduction of these types of T cells may lead to uncontrolled innate immune responses and unchecked inflammatory responses (Qin et al., 2020). Indeed, excessive activation of monocyte/macrophage and cytokine storms are linked with the gravity of the disease and the related complications in SARS-CoV-2 infection (Fung et al., 2020; Giamarellos-Bourboulis et al., 2020).

The study on 28 patients with SARS-CoV-2 infection showed an alteration in the morphology and action of monocytes/macrophages as a predictive value for the severity of the disease, potential risk of intensive care unit (ICU) admission, length of stay in the hospital, and full recovery (Zhang et al., 2020).

Mature macrophages can alter their phenotypes and undergo functional polarization in response to signals from the local microenvironment that induce naïve or resting "M0 macrophages" to adopt classically activated "M1-like" or anti-inflammatory "M2-like" phenotypes or promote M1-like and M2-like macrophage interconversion. M1 macrophages secrete elevated levels of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, to regulate local tissue and immune responses that promote pathogen clearance. Elevated serum levels of IL-6, a hallmark of severe SARS-CoV-2 infections, correlate with ARDS, respiratory failure, and adverse clinical outcomes in COVID-19 patients (Jingping Liu, Li, et al., 2020).

The genome of SARS-CoV and MERS-CoV translates multiple proteins, which contribute to antagonizing the IFN responses, with preliminary antagonism of IFN resulting in delayed or evaded innate immune responses (Channappanavar & Perlman, 2017; Channappanavar et al., 2016). Followed by postponed IFN cascade, the inflammatory monocyte/macrophage responses are further organized and T cells are sensitized to apoptosis; as a result, the dysregulated inflammatory response is more activated (Channappanavar et al., 2016). These inflammatory macrophages (M1) accumulate in the lungs; they are the potential sources of proinflammatory cytokines and chemokines associated with fatal diseases induced by human coronavirus infections such as SARS and COVID-19. The autopsy findings of COVID-19 are correlated with these consequences (Yao et al., 2020).

Remarkably, the monocytes isolated from infected patients are identified to be angiotensin-converting enzyme 2 (ACE2)-positive cells. The ACE2 receptors are utilized by SARS-CoV-2 to invade the host cells, suggesting the probability of direct infection of monocytes in COVID-19 patients and leading to abortive replication of the virus and postponed type I IFN signaling in these types of cells (Acharya et al., 2020). As was shown earlier, monocyte infection by SARS-CoV was responsible for the activation of inflammatory responses and altered gene expression related to the immune system signaling (Dosch et al., 2009; Hu et al., 2012).

The differentiation of monocytes to macrophages is induced by inflammatory mediators, e.g. GM-CSF, IFN-α, IL6, or TNF-α. Recently, Y. Zhou et al. (2020) demonstrated that severe pulmonary syndrome patients admitted in ICU had a higher percentage of $CD14^+CD16^+$ monocytes. In addition, the ability of these monocytes in the production of mediators, such as GM-CSF and IL6-associated with cytokine storm, has been proven. A model also was defined by this study group, whereby an abnormal Th1 response activates GM-CSF induced monocyte/macrophage, correlated by enhanced IL6 $CD14^+$ $CD16^+$ producing monocytes. Then, these monocytes migrate into the lung tissue and along with an inflammatory cytokine storm induce the subsequent lung injury. This condition was additionally supported by the recent data from a study performed on single-cell RNA sequencing on the immune cells isolated from bronchoalveolar lavage samples of COVID-19 patients that provide critical insights into the immune microenvironment of the infected pulmonary tissue (Liao et al., 2020; Schulte-Schrepping et al., 2020). There was an increase in HLA-$DR^{hi}CD11c^{hi}$ inflammatory monocytes with an interferon-stimulated gene effect in mild COVID-19. Severe COVID-19 was signaled by the incidence of neutrophil precursors, as evidence of serious myelopoiesis, dysfunctional mature neutrophils, and HLA-DR^{lo} monocytes (Schulte-Schrepping et al., 2020).

The main macrophage subset in the lungs of patients with ARDS was proven to be alveolar macrophages expressing supplant fatty acid binding protein-4 (FABP4) and the Ficolin 1 expressing monocyte-derived macrophages. These cells are highly implicated in the inflammatory responses and produce a wide range of chemokines involved in a cytokine storm (Qin et al., 2020). This evidence confirms the movement of inflammatory monocyte/macrophages into the lung tissue and other infected organs. On the other hand, there is a nonspecific finding demonstrating that somewhat larger, vacuolated, and atypical monocytes were observed in the morphological assessment of peripheral blood films of infected patients (Zhang et al., 2020).

4 | FUNCTIONAL EXHAUSTION OF ANTIVIRAL LYMPHOCYTES IN SARS-COV-2

Several studies have proven a remarkable decrease in the total number of natural killer (NK) and $CD8^+$ T cells in COVID-19 patients. Also, the exhausted activation of NK and $CD8^+$ T cells due to enhanced expression of CD94/NK group 2 member A (NKG2A) was observed in these cases. Notably, the enhanced number of NK and $CD8^+$ T cells was correlated with decreased NKG2A expression after therapy and gradual recovery in patients, suggesting that the functional exhaustion of CTLs is related to SARS-CoV-2 infection (Diao et al., 2020). Moreover, $CD8^+$ T cells and $CD4^+$ T cells have higher levels of PD-1 and Tim-3, exhaustion markers, in patients (Diao et al., 2020; H.-Y. Zheng et al., 2020). In the early stages, SARS-CoV-2 infection may break down antiviral immunity (N. Chen et al., 2020; R. Zhou et al., 2020). Importantly, the effects of NKG2A expression on NK and $CD8^+$ T cells activation lead to functional depletion of NK and CTLs. According to results, NKG2A expression was upregulated on NK cells and $CD8^+$ T cells in COVID-19 patients with a reduced ability to produce CD107a, granzyme B, IFN-γ, and TNF-α (Haanen & Cerundolo, 2018).

The number of $NKG2A^+$ cytotoxic lymphocytes was also reduced in recovered COVID-19 patients, emphasizing the important role of

NKG2A expression in the pathogenesis of COVID-19 in the early stage, correlated with the functional exhaustion of cytotoxic lymphocytes and progression of the disease (Haanen & Cerundolo, 2018).

Exhausted NK cells and $CD8^+$ T cells arise from during chronic conditions such as chronic infection and tumorigenesis. Also, T cell apoptosis with identical underlying mechanisms was observed both in chronic infection and cancer. This condition was also proven in patients with SARS-CoV infection (Barathan et al., 2018). Therefore, exhaustion of $NKG2A^+$ cytotoxic lymphocytes may be predicted in patients with SARS-CoV infection. In addition, effective control of SARS-CoV-2 infection is dependent on the decreased expression of NKG2A in cytotoxic lymphocytes, as the percentage of $NKG2A^+$ cytotoxic lymphocytes was reduced following the antiviral therapy (94% of patients were administered antiviral therapy [Kaletra]) in the patients with COVID-19. Consequently, SARS-CoV-2 infection-induced NKG2A expression may be correlated with the functional exhaustion of cytotoxic lymphocytes at the early stage in COVID-19 patients with severe pulmonary inflammation, leading to the progression of the illness (M. Zheng et al., 2020).

5 | DYSREGULATION OF COMPLEMENT SYSTEM IN SARS-COV-2

The complement system plays a pivotal role in the host immune response to COVID-19. Complement activation was also observed in COVID-19 patients, which might be involved in the pathogenesis of severe lung injury and ARDS. Furthermore, complement activation may contribute to the maladaptive inflammatory and immune response rather than increased viral loads seen in some patients with acute COVID-19 (Guan et al., 2020; Li et al., 2020).

The virus uses virus-encoded proteins to avoid being detected by the complement system, emphasizing the critical role of complements in antiviral responses. C3a and C5a with potential characteristics of proinflammatory factors are able to initiate the recruitment of inflammatory cells and activate neutrophils (Gralinski et al., 2018).

As a curative approach to acute lung injury, the obstruction of C3a and C5a has been proved to be fruitful. Anti-C5a antibody was reported to mitigate the gravity of the adverse impacts arising from MERS-CoV in mice (Gralinski et al., 2018; Sun et al., 2013). In a study by Gao et al. (2020) N proteins were shown to empower SARS-CoV-2 to attach to mannose-associated serine protease 2 (MASP-2). MASP-2 is a key serine protease in the lectin pathway of complement activation, resulting in aberrant C5 activation and aggravated inflammatory lung injury. The complement cascade is activated during SARS-CoV-2 and participates in the pathogenesis of the disease (Gao et al., 2020; Sun et al., 2013).

6 | CONCLUSION

SARS-CoV-2 can evade the immune responses, which permits the virus to produce enormous copy numbers in infected tissues. Through the dysregulation and infection of the immune cells as well as the recruitment of other immune cells from the circulation to the site of infection, acute immune reactions induce inflammation resulting in a cytokine storm and life- menacing problems (Schurink et al., 2020; Yazdanpanah et al., 2020). Dysregulation of host immunity, including hyper-activation of macrophage and complement system, NLR induction, as well as NK cells and CTLs exhaustion, could be involved in the disease severity and outcomes. Understanding of the immune system dysregulation seems to be critical for disease control in patients with COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHORS CONTRIBUTIONS

N. R. proposed the general concept and supervised the project. L. M. K. contributed to the data gathering, writing the manuscript, and preparing the figure, while N. R. contributed to study design, scientific, and structural editing. N. R. and L. M. K. critically revised the manuscript. Both authors approved the final draft of the manuscript before submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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