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Review

Immune responses to SARS-CoV-2 infection in Humans and ACE2 humanized mice

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents a major public health threat worldwide. Insight into protective and pathogenic aspects of SARS-CoV-2 immune responses is critical to work out effective therapeutics and develop vaccines for controlling the disease. Here, we review the present literature describing the innate and adaptive immune responses including innate immune cells, cytokine responses, antibody responses and T cell responses against SARS-CoV-2 in human infection, as well as in AEC2-humanized mouse infection. We also summarize the now known and unknown about the role of the SARS-CoV-2 immune responses. By better understanding the mechanisms that drive the immune responses, we can tailor treatment strategies at specific disease stages and improve our response to this worldwide public health threat.

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak began in December 2019 and is caused by the respiratory viral pathogen severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2). As of Dec 12, 2020, SARS-CoV-2 has infected at least 71 million individuals and killed more than 1,596,367 people globally, and counting. Clinical symptoms of COVID-19 range from asymptomatic or mild disease frequently observed in children and younger adults to severe clinical symptoms associated with high mortality mainly in elderly and high-risk patients. These pathological disparities are probably resulting from differences in the immune response to SARS-CoV-2. Severe disease characterized by severe respiratory failure [1], as well as the fact that some patients' symptoms suddenly worsen around one week after symptom onset, suggests that dysregulated immune reactions contribute to COVID-19 pathogenesis. A better understanding on the immune response to SARS-CoV-2, especially deciphering those protective and detrimental components, will offer important insights into treatment and management of the disease, including new therapies and vaccine development.

This review will cover what is currently known about the innate and adaptive immune responses to SARS-CoV-2 infection in human and mouse models, focusing on those studies that potentially provide insight into the COVID-19 immunity landscape.

2. Innate immune responses

The innate immune system is the first responders in detecting and clearing viral infections. Multi-types of innate immune cells including granulocytes, monocytes, macrophages, neutrophils, dendritic cells (DC), and natural killer (NK) cells work together to provoke antiviral function in the host. Upon stimulation, these cells can secrete proinflammatory cytokines to inhibit viral replication, stimulate the adaptive immune response, and recruit other immune cells to the infection site [2].

Though SARS-CoV-2 like SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as its receptor for entry in target cells, also considered as highly pathogenic coronavirus, the innate immune response and cytokine profiles induced by the two viruses are different.

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2.1. Neutrophils

As recently reported [3], the COVID-19 patients of the present cohort showed not only lymphopenia but also significant neutrophil. Thus, elevated neutrophil levels may be useful for predicting the severity of disease; the neutrophil-to-lymphocyte ratio (NLR) is a simple biomarker of inflammation that can be measured during routine hematology [4]. Aijia Ma et al. revealed that NLR could be a valuable biomarker to recognize severe COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS), which facilitated clinicians to give effective respiratory supporting strategies.

Although COVID-19 patients show higher neutrophil levels, how neutrophil affects the inflammatory response leading to more severe symptoms remains unclear. Recently, Meng Wu et al. [5] identified activated neutrophil from the lung tissue obtained from patients who died of COVID-19, suggesting that neutrophil may play an important role in the lungs. Among the effector mechanisms of neutrophils in inflammatory diseases, neutrophil-derived extracellular traps (NETs) play a critical role. NETs are networks of extracellular fibers composed of DNA containing histones and granule-derived enzymes, such as myeloperoxidase (MPO) and elastase, which contribute to inflammation-associated lung damage, thrombosis, and fibrosis. Not surprisingly, they were also found in the lungs of severe COVID-19 patients, infiltrating the lung airway, interstitial, and vascular compartments [6]. Moreover, Flavio Protasio Veras et al. [7] discovered that SARS-CoV-2 can directly induce the release of NETs by neutrophils, depending on ACE2, serine protease, virus replication, and protein arginine deiminase 4 (PAD-4). What's more, the NETs released by SARS-CoV-2–activated neutrophils increase the risk of lung epithelial cell death *in vitro*, as shown in **Figure**.

In addition, several studies [8,9] have shown that NETs are highly associated with immunothrombosis. A hypercoagulability state has been reported as a major pathologic event in COVID-19, and thromboembolic complications listed among life-threatening complications of the disease. Through further study, Panagiotis Skendros et al. [8] believed that complement and tissue factor — enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis, and they hypothesized that the activated complement can activate neutrophil, which would release NETs carrying the active tissue factor (TF) to induce endothelial cell activation toward TF expression, thus increasing their procoagulant activity, as shown in **Figure**.

Some researchers [10] believed that neutrophils aggravate the disease not only through NETs, but also through releasing excessive levels of reactive oxygen species (ROS), which can induce tissue damage, thrombosis and red blood cell dysfunction, as shown in **Figure**. Despite limited investigations on neutrophils, a number of researchers have suggested that neutrophils may serve as potential therapeutic targets of COVID-19.

2.2. Natural killer cells (NK cells)

Among the studies on NK cells, many [11–14] focus on the significantly impaired NK cell counts but not the NK cell frequency observed in COVID-19 patients. They believe NK cells are hyperactivated in the acute phase of COVID-19, but return to the normal level after clinical recovery from COVID-19. Does the frequency of $CD56^{bright}$ immature NK cells decrease? Does the frequency of $CD56^{dim}$ mature NK cells increase? Is NK function impaired in COVID-19? These questions remain unanswered. Stefania Varchetta et al. [11] and Mohammed Osman et al. [12] both observed a reduction of immature NK cells and a parallel enrichment in the mature subset. Of note, a significant reduction of IFN-γ secretion and degranulation activity, related to cytolytic activity, was observed in NK cells, which could be associated with exhaustion of NK cells. Christopher Maucourant et al. [13] deem that the frequency of mature and immature NK and the function of NK cells do not change, as shown in **Figure**. It is severe, but not moderate, COVID-19 disease that is associated with higher frequencies of adaptive NK cells that display signs of proliferation and activation without detectable concurrent CMV reactivation. Their conclusion needs to be further evidenced.

2.3. Dendritic cells (DCs)

DCs are professional antigen-presenting cells and represent either the key components of innate response to pathogen infection or the orchestrators of the subsequent adaptive immunity. Previous studies on DCs, either by single-cell RNA-sequencing [14] or by flow cytometry [15], have shown a significant DCs reduction in COVID-19, where not only the total DCs but also the composition of DC subsets altered. Runhong Zhou et al. [15] showed that ratios of conventional DCs to plasmacytoid DCs were increased among acute severe patients. They also demonstrated that patient-derived DCs reduced their functionality of maturation with a lower expression amount of the co-stimulatory molecule CD86, either in the acute or convalescence phase. At the same time, *ex vivo* experiments indicated that DCs derived from the acute phase were functionally impaired, which activated type I interferon and T cells, thus likely reducing the induction of adaptive T cell responses against SARS-CoV-2. Later studies yielded similar results [16], as shown in **Figure**.

Besides PBMCs of patients, the effects of viruses on DC have also been studied. Dong Yang et al. [17] proved that monocyte-derived dendritic cells (moDCs) could be abortively infected by SARS-CoV-2, which did not activate IFN type I, II, or III response and proinflammatory response, and antagonized STAT1 phosphorylation simultaneously in moDCs, as shown in **Figure**. All these studies consistently agree that DCs are in a functional inhibitory state in SARS-CoV-2 infections.

2.4. Monocytes and macrophages

Monocytes and macrophages, playing essential roles in innate immunity and the regulation of adaptive immunity, can not only produce cytokine responses but also act as antigen presenting cells like DCs.

During SARS-CoV-2 infection, monocytes play an important role in peripheral immunity. A previous study [18] using single-cell RNA-sequencing has identified a monocyte subpopulation that contributes to the inflammatory cytokine storms, specifically during the severe stage of COVID-19. Results from both this and another report [19] agreed that these inflammatory monocytes could release IL-6, which was an essential component of inflammatory storm in severe COVID-19 patients. In addition, these severe-stage monocytes expressed elevated levels of IL-1β and its receptor, and chemokines such as CCL4L2, CCL3, and CCL4 and their respective receptors. Even in recovery stages, early or late, COVID-19 patients were reported to have more $CD14^{++}IL\text{-}1\beta^{+}$ and IFN-activated monocytes in their peripheral blood than healthy controls [20]. Intriguingly, a population of myeloid-derived suppressor cells (MDSCs)-like monocytes, which correlated with lymphopenia and inflammation in the blood of severe COVID-19 patients, were found to be immune-paralyzed [21]. Besides, a study on the combination of COVID-19 and type II diabetes (T2D) [22] revealed that a morphological anomaly of increased monocyte size and monocytopenia restricted to classical $CD14^{high}CD16^{-}$ monocytes was specifically associated with severe COVID-19 in patients with T2D requiring intensive care. Obviously, all these studies suggested that significant dysregulation of monocytes seems to be a feature of COVID-19. How these remarkable changes in monocytes affect COVID-19, however, remains largely unknown. Of note, Eugenio Hottz et al.'s study [23] on effects of monocytes uncovered that platelet-monocyte interaction and platelet-dependent monocyte TF expression promote the hypercoagulability state in COVID-19 patients, which were associated with COVID-19 severity and mortality.

Unlike monocytes, macrophages act mainly *in situ*. Monocyte-macrophages in BALFs of COVID-19 patients were found to produce massive amounts of cytokines and chemokines, but secrete little interferon [21]. Autopsy reports [24] indicated that inflammatory macrophages accumulated in the lungs of COVID-19 patients. Mingfeng

Liao et al. [25] found a highly proinflammatory macrophage microenvironment presenting in the lungs of patients with severe COVID-19. Simultaneously, they demonstrated that IL-1β, IL-6, TNF and various chemokines (CCL2, CCL3, CCL4 and CCL7) were expressed at higher levels in lung macrophages from patients with severe COVID-19 infection, and CXCL9, CXCL10 and CXCL11 levels were much higher in both COVID-19 groups than in healthy people, but CXCL16, whose product binds CXCR6, was expressed at higher levels in moderate infection than in severe infection, as shown in **Figure**.

Dong Yang et al. [17] revealed that macrophages could be abortively infected by SARS-CoV-2, initiate an attenuated interferon response, and subsequently express significant proinflammatory cytokine/chemokine, as shown in **Figure**. Thereby in COVID-19, macrophages may also serve as a Trojan horse, enabling viral anchoring specifically within the pulmonary parenchyma. Reallocation of viral-containing macrophages migrating out of the lung to other tissues is theoretically plausible in the context of viral spread with the involvement of other organs [26], but this is still an unproven hypothesis.

2.5. Cytokine responses

Since the outbreak of COVID-19, many studies have been conducted on cytokine responses. Several studies have reported an association between progression to severe COVID-19 and dysregulated secretion of proinflammatory cytokines. A cohort study [27], by enrolling 50 COVID-19 patients, showed that fourteen cytokines including IL-1β, IL-1ra, IL-6, IL-13, IL-18, HGF (hepatocyte growth factor), MCP-3 (monocyte chemotactic protein-3), MIG (monokine induced gamma interferon), M-CSF (macrophage colony stimulating factor), G-CSF (granulocyte colony-stimulating factor), MIP-1α (macrophage inflammatory protein 1 alpha), MIP-1β, CTACK (cutaneous T-cell-attracting chemokine) and IP-10 (interferon gamma induced protein 10) were elevated in COVID-19 patients, as shown in **Figure**. Among them, the expression levels of IP-10, MCP-3, HGF, MIG and MIP-1α were remarkably higher in critically ill patients. Another cohort study [28], by enrolling 326 COVID-19 patients, suggested that IL-6 and IL-8 were significantly higher in the critical group. Carolina Lucas et al. [29] demonstrated that IL-6, IFN-α, CCL1, IL-18, IFN-λ, IL-17A, IL-5, IL-13 and IgE increased in critical patients. All these data highlight the broad inflammatory changes in COVID-19, especially in severe or critical patients, making many scientists believe that SARS-CoV-2 infection induces cytokine storm. Actually, whether cytokine storm occurring after SARS-CoV-2 infection remains controversial. Very recently, a meta-analysis on COVID-19 has come to a different conclusion [30]. This analysis indicated that the elevation of inflammatory cytokines would occur in COVID-19, but the elevated levels of inflammatory cytokines including IL-6, IL-8, TNF are profoundly lower than those reported in patients with acute respiratory distress syndrome (ARDS) unrelated to COVID-19, sepsis, and chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome. Thus, the hypothesis about cytokine storms may be inaccurate; the immune features of COVID-19 need to be further studied.

3. Humoral immune responses

Humoral immunity, also called antibody-mediated immunity, is essential for host defense. Typically, B cells are produced by the bone marrow and circulate through body fluids. Once upon the infection of SARS-CoV-2, B cells of COVID-19 patients differentiate into memory B and plasma cells releasing antibodies. Antibodies produced by the plasma cells can target invading pathogens for destruction via multiple defense mechanisms, including neutralization and activation of the complement system [31]. As for SARS-CoV-2 infection, COVID-19 patients' immune response to the SARS-CoV-2 significantly varies with disease severity, age, etc. Owing to the lack of specific drugs, the majority of treatments for COVID-19 patients are supportive. Tracking patients' humoral responses over time may shed light on the treatment for patients and benefit the development of optimal vaccines.

A stereotypical naive B cell immune response to SARS-CoV-2 was observed in COVID-19 patients, showing a remarkable increase in the plasma cells and a decrease in the naïve B cells, as shown in **Figure**. B cell clonal expansion was observed during infection and the dominant expansion showed decreased diversity following recovery from infection [21]. There were strong convergent B cell responses to SARS-CoV-2 epitopes which were predominantly naïve. Therein converging IGHV3-driven BCR clusters were closely associated with SARS-CoV-2 antibodies [32].

According to previous reports concerning the SARS epidemic, IgM response against SARS-CoV antigen (S and N proteins) reached a peak within four weeks and was no more detectable 3 months post symptoms onset; the switch to IgG often occurred around two weeks later, and IgG could be detectable within three years [33]. Similarly, the dynamics of the antibody profile in COVID-19 patients showed that IgG responses were detected in most patients, including both the severe and mild groups, between 8 and 12 days post onset; SARS-CoV-2 IgM and IgG response reached a peak in about 2 and 3 weeks [34], remained at a high level for over 60 days, then declined within 90 days [35]. IgM plays a dominate role in the neutralizing titer early in the infection [36]; compared with severe patients, the mild group showed much lower IgM response. Antibodies cross-reactive to SARS-CoV and SARS-CoV-2 were detected in patients with COVID-19 but not in patients with MERS. No obvious cross-reactivity from other human coronaviruses was detected, including OC43, 229E, HKU1, NL63.

Neutralizing antibodies play critical roles in blocking viral replication, contributing to viral clearance during acute infection. Most of SARS-CoV-2 showed typical acute infection characterization or feature. The receptor binding domain (RBD) is the main target for antibody-mediated neutralization. High levels of neutralizing antibodies were induced about 10-15 days post onset in both severe and mild patients. Both severe and mild patients showed similar kinetics of the nAb response, but with the magnitude of the nAb response positively related with the disease severity [35]. Declining nAb titers were observed following the nAb titer peak. It is necessary to define durability of nAb protection against re-infection with SARS-CoV-2 and the vaccine protection. Neutralizing Abs in the plasma of recovered COVID-19 patients could be employed in the passive antibody therapy for SARS-CoV-2 infected patients. Based on some observational data, administration of convalescent plasma containing neutralizing antibodies may be beneficial in the treatment of critically ill patients [37]. A recent randomized trial of convalescent plasma, however, observed no significant differences in the clinical status or overall mortality between patients treated with convalescent plasma and those receiving placebo [38].

As for the cross-reaction among CoVs, recent reports indicated that COVID-19 patients developed high titers of the neutralizing Abs targeting domain including S1, RBD and S2 domains. Interestingly, these neutralizing Abs had cross-reactivity but no efficiently neutralizing activity against SARS-CoV [39]. Paradoxically, cross-neutralization monoclonal antibodies (S309)) against both SARS-CoV-2 and SARS-CoV were discovered from SARS convalescents [40]. Serum antibodies from recovered SARS patients and immunized animals could cross neutralize SARS-CoV-2 [41], but owing to the antibody titer declining after more than 15-17 years, most of SARS-CoV convalescents' plasma could not efficiently neutralize SARS-CoV-2 [42]. Age and disease severity may be considered covariates in relation to the development of neutralizing antibodies. Elderly and middle-aged patients displayed higher titers of neutralizing Abs than younger patients [39]. Severe patients showed a prolonged stage of neutralizing Abs than the mild or asymptomatic ones. Some COVID-19 convalescents were tested RNA positive for SARS-CoV-2 after discharge. Whether patients can be re-infected by the virus after they have recovered from the primary infection remains a question. One feature of SARS-CoV-2 infection is the prolonged virus shedding. The latest research indicated that the median carrying history of long-

term carriers was about 92 days after the first admission, and the longest carrying history was more than 100 days [43]. Genome and antibody response analysis showed that the virus sequences obtained in the second infection matched early viral strains, and a similar antibody profile was detected between long-term carriers and recovered patients, indicating the patients persistently carrying the virus may not be re-infected [43].

4. T cell immune responses

T cells, which dominate the adaptive cellular immunity, play crucial roles in the immune response to viral infection. During the infection, macrophages and neighboring endothelial and epithelial cells in the airway recognize damage-associated molecular patterns molecules released by infected cells, and produce pro-inflammatory cytokines, including chemokines such as IL-6, IP-10, MIP-1a, MIP-1b and MCP-1, to recruit monocytes, macrophages, and T cells to the infection site and promote further inflammation. Interferon gamma (IFN-γ) is one of the dominant cytokines produced by T cells, which plays a key role in controlling viral infection.

Several T cell types are involved in the antiviral response, as shown in **Figure**. $CD8^+$ T cells recognize viral peptides presented at the surfaces of infected cells and drive cytotoxic response to directly kill them, thus stopping the spread of virus in consequence. While $CD4^+$ T cells respond to the infection in several ways. In a way of cell-cell interactions and cytokines releasing, $CD4^+$ T cells can help B cells for humoral immune responses, termed to a specialized subset as follicular helper T (Tfh) cells. Another imperative function of $CD4^+$ T cells is to regulate functions of other immune cells including $CD8^+$ T cells and macrophages. Because T cell dysfunction may cause immunopathology and tissue damage, clarifying the T cell immunity will provide a solid foundation for the understanding and application of T cells to antiviral immunotherapy in approaches. Generally, an incubation time of 7 to 10 days is needed for adaptive T cells priming and expanding in numerous primary viral infections, which is coincident with the typical time that COVID-19 patients take to recover or to develop severe illness [44].

5. T cell lymphopenia in COVID-19

Lymphopenia is one prominent feature of SARS-CoV-2 infection, remarkably in severe infection, and would resolve when patients recover. lymphopenia in COVID-19 seems more severe and lasts longer than many other respiratory viral infections, such as influenza A H3N2 virus and human respiratory syncytial virus, and displays a bias towards T cell lineages, even though B cells and NK cells have been reported to be affected in some patients. Numerous studies have illustrated that numbers of both peripheral $CD4^+$ T cells and $CD8^+$ T cells reduced in moderate and severe COVID-19 patients [1,45–48]. Furthermore, lymphocyte counts have prognostic value, as the frequencies of $CD3^+$ T cells and $CD8^+$ T cells in the peripheral blood have been proved to be correlated with severity of COVID-19 patients, predicting the transition from mild to severe illness [46,48,49]. A rational interpretation of decreased peripheral T cells could be that T cells are recruited to the infected sites to control the virus. Supporting this hypothesis, a single-cell sequencing study has revealed that $CD8^+$ T cells with clonal expansion increase in bronchoalveolar lavage fluid (BALF) of patients with COVID-19 [25]. Consistently, autopsy of a COVID-19 patient showed that T cells accumulated in the lungs, along with lower levels of T cells in the blood [50], although another study only found neutrophils infiltration in the lung through postmortem core biopsies [51]. Indeed, inflammatory cytokines may contribute to the loss of circulating T cells with the results showing that tocilizumab, an IL-6 receptor antagonist, could increase the number of lymphocytes in the blood [52]. The lower proinflammatory cytokines were observed to be correlated with restored bulk T cell frequencies in convalescent patients with COVID-19 [48,53–55]. All these results have made some contributions to understanding the mechanism of lymphopenia. The relevant cause and effect of this common phenomenon still need further exploration.

6. CD4 T and CD8 T cell responses in COVID-19

It is commonly recognized that T cells are highly activated after SARS-CoV-2 infection, accompanied by the expression of HLA-DR, CD38, CD69, CD44 and CD25 [25,56–58]. What's more, these T cells are proliferating, as they express high levels of Ki-67 [57,59]. Additionally, the expression of several inhibitory markers, including PD-1, TIM-3, CTLA-4, TIGIT and NKG2a, has been shown up-regulated in T cells from COVID-19 patients [48,59,60], which indicates they tend to be exhausted and functionally impaired. Consistently, the frequencies of polyfunctional T cells have been shown to significantly reduce in critically ill patients with COVID-19 [48,59,61]. Similarly, $CD8^+$ T cells down-regulated the expression of functional molecules, such as CD107a and granzyme B (GzmB) [48]. Controversial results from another study, however, showed that $CD8^+$ T cells up-regulate GzmB and perforin expression in severely sick patients [59]. A single-cell sequencing study of BALF has further demonstrated that CD8 T cells expressed high levels of GZMA, GZMB and GZBK in sever patients, while they expressed KLRC1 and XCL1 in mild patients [25]. Collectively, the phenotype and functional status of T cells, to a large extent, determine their ability to control virus infection.

Notably, while controlling viral infection, T cells may also contribute to COVID-19 hyperinflammation. It has been found that ICU patients with more severe pneumonia showed a correlated higher percentage of $GM\text{-}CSF^+$ $CD4^+$ T cells [60], which has previously proved to be pathogenic in different kinds of inflammatory autoimmune disorders [62]. Apart from increasing proinflammatory pathogenic Th subsets, regulatory T cells (Tregs), a subset with remissive function in ARDS inflammation [63], get reduced in severe COVID-19 patients [1,64].

SARS-CoV-2-specific T cells from severe infections tended to have a central memory phenotype with a significantly higher frequency of polyfunctional CD4+ T cells with cytokine secretion, including IFNγ, TNFα, and IL-2, and CD8+ T cells with cytokine secretion, such as IFNγ, TNFα and degranulated state, as compared with mild infections [65]. SARS-CoV-2–specific T cells can be expanded from convalescent donors and recognize immunodominant viral epitopes in conserved regions of membrane, spike, and nucleocapsid, as well as nsp3, nsp4, ORF3a, and ORF8 proteins [66]. Recent reports have also suggested that immunocompromised patients may be at high risk of severe and potentially prolonged disease, suggesting that T-cell immunity is essential for overcoming COVID-19 [67].

7. Unconventional T cell responses in COVID-19

Besides classic adaptive CD4+ and CD8+ T cells, unconventional T cells comprise mucosa-associated invariant T (MAIT), $\gamma\delta$T, and invariant natural killer T (iNKT) cells and mainly populate mucosal tissues, including the lung. Circulating unconventional T cells of COVID-19 patients presented with a profound and preferential decline paired with strong activation, and activated unconventional T cells populated the airways of patients displaying strong local inflammation [68,69]. In addition, expression of the CD69 activation marker on blood iNKT and MAIT cells of COVID-19 patients on admission could be a prediction of clinical course and disease severity[68]. All the above results indicated that T cell functions are highly determined by the microenvironment where they stay, and the comprehensive understanding of the dynamics and functions of T cells in SARS-CoV-2 infection might be more therapeutically meaningful.

8. Immune responses to SARS-CoV-2 in mice

Laboratory mice are essential tools to clarify the characteristics and mechanisms of virus-induced immune response; however, they do not

support infection by SARS-CoV-2 due to the virus's inability to use the mouse angiotensin-converting enzyme 2 (mACE2), which is the orthologue of human entry receptor angiotensin-converting enzyme 2 (hACE2). To solve this problem, some strategies have been developed, such as expression of hACE2 in genetically modified mice, delivery of hACE2 by the replication defective vector, adaptation of SARS-CoV-2 to mACE2. Thereafter, the immune response induced by SARS-CoV-2 in mice has gradually been revealed.

9. Innate immune responses to SARS-CoV-2 in mice

SARS-CoV-2 infection induces obvious and delayed type-I interferon (IFN) responses as compared with Sendai virus *in vitro*, and NSP1, NSP3, NSP12, NSP13, NSP14, ORF3, ORF6, and M inhibited IFN-β activation significantly, but S and NSP2 protein performed the opposite effects. Even so, SARS-CoV-2 is sensitive to IFN-β treatment [19], decreased viral RNA and viral titer. AAV-hACE2 and Ad5-hACE2 transduced mice or K18-hACE2 mice infected with SARS-CoV-2 displayed expansion of pulmonary infiltrating myeloid-derived inflammatory cells monocytes, macrophages, T cells and B cells [70]. In addition, natural killer (NK) cells expanded at the early infection period. Type I IFN signaling influences the recruitment of monocytes and macrophages into the lungs as well as the antiviral ISG expression [71]. Treatment with the interferon inducer, such as Poly I:C, decreased the SARS-CoV-2 viral titer in the lungs of Ad5-hACE2 transduced mice [72]. Clinical trials using IFN-I alone or in combination with other antivirals are currently under way for COVID-19 patients in several hospitals. Treatment with interferon (IFN)-a2b for the confirmed COVID-19 cases significantly reduced the duration of the detectable virus in the upper respiratory tract and the levels of inflammatory markers IL-6 and CRP in the blood [73]. The triple combination of IFNβ-1b, lopinavir–ritonavir, and ribavirin was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay for patients with mild to moderate COVID-19 [74]. It has to be noted that all these patients were treated in the early stages of the disease. Timing of IFN-I treatment is very important in Coronavirus infection [74].

10. Humoral immunity in mice

Humoral immune response plays an important role in the control of infection. Along with the establishment of SARS-CoV-2 mouse models, the humoral immune response in mice induced by the SARS-CoV-2 has been analyzed. SARS-CoV-2 specific binding antibodies were first detected in hACE2 transgenic mice. Specific IgG antibodies against the spike (S) protein of SARS-CoV-2 in the sera of infected hACE2 mice were detected at 21 dpi, but not in wild type (WT) control mice [75]. Another paper shows that surviving SARS-CoV-2 infected hACE2 transgenic mice generated low titers of neutralization antibodies (1:10–1:40), which might contribute to the protection from reinfection [76]. Sun et al. showed that neutralizing antibodies in sera after infection peaked at day 10 post infection (10 d.p.i.) in Ad5-hACE2-sensitized mice [77]. SARS-CoV-2 specific IgM was investigated in SARS-CoV-2 infected K18-hACE mice (transgenic mice expressing the hACE2 under a cytokeratin 18 promoter (K18), hereafter, K18-hACE mice), and SARS-CoV-2 spike-specific IgM in serum could be detected at 3 and 7 d.p.i.

11. Immune cell responses in mice

Immune cell responses are also induced in SARS-CoV-2 infected mice besides antibody responses. Infiltration of inflammatory cells into the lung interstitium has been clinically manifested in SARS-CoV-2 infection. Existing mouse models have explained lung inflammatory cell infiltration through pathological analysis, but rarely mouse T cell responses. The infiltration of lymphocytes into the lungs of SARS-CoV-2 infected mice was first clarified in hACE2 transgenic mice. $CD3^+$ T lymphocytes were dispersed or (occasionally) aggregated in the alveolar interstitium at 3 and 5 d.p.i., and some $CD19^+$ B lymphocytes were also observed in immunohistochemistry (IHC) staining of lung sections at 5 d.p.i. [75]. In SARS-CoV-2-infected K18-hACE2 mice, the numbers of $CD45^+$ immune cells trended to be higher in the BAL beginning at 2 d.p.i. and in the lung at 4 d.p.i., without statistical significance; by 7 d.p.i., lymphoid cell subsets increased in the lung, including $NK1.1^+$ natural killer cells, $\gamma\delta$ $CD3^+$ T cells, $CD3^+CD4^+$ T cells, $CD3^+CD8^+$ T cells and activated $CD44^+CD3^+CD8^+$ T cells by flow cytometric analysis [78]. Contrast to the lymphocytes increasing in the lung, the number of B cells, CD4+ T cells, CD8+ T cells and monocytes in the peripheral blood markedly decreased in K18-hACE2 mice at 5 d.p.i., accompanied by an increased neutrophil-to-lymphocyte ratio, similar to COVID-19 patients [78]. As evidenced by Emma S. Winkler, Venezuelan equine encephalitis replicon particles (VEEV-VRP-hACE2)-transduced, SARS-CoV-2-infected mice had a higher neutrophil-to-lymphocyte ratio in the peripheral blood at 2 dpi compared with control mice [79]. All these studies focused on lymphocyte responses to SARS-CoV-2 byanalyzing bulk T cells rather than SARS-CoV-2 specific T cell responses. Sun et at first uncovered SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cell responses in the replication-deficient adenovirus (Ad5-hACE2)-sensitized mouse model (results published in *Cell*). $CD4^+$ and $CD8^+$ T cell epitopes of SARS-CoV-2 were predominantly located in the N protein and the S1 region of the S protein, respectively, in BALB/c mice, and virus-specific T cell responses peaked at 8 d.p.i. What's more, They pointed out that the optimal virus clearance required both $CD4^+$ and $CD8^+$ T cell responses in SARS-CoV-2 infected mice [77]. SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cell epitopes were mapped both in C57BL/6 mice and in BALB/c mice [80]. Similar to virus-specific T cells in SASRS-CoV and MERS-CoV infections, SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cells protect mice from SARS-CoV-2 infection[80]. Virus-specific T cells are durable in the host, and epitopes of T cells are relatively conserved, which is useful for novel vaccine development. Uncovering the function of virus-specific T cells and its mechanisms are in urgent need.

12. Conclusions

COVID-19 is still circulating worldwide and being life threatening to patients with pre-existing medical health conditions, such as chronic inflammatory disorders and immunodeficiency. Intra-individual differences in the host immune defense against SARS-CoV-2 infection have been broadly reported in clinical research. Joint efforts have been devoted to deepening the scientific understanding of immune responses against the infection, but much remains to be elucidated. Although two risk factors, old age and male sex, have been determined to be correlated to COVID-19 severity, the underlying mechanisms of disease heterogeneity are far from clear. Based on the current literature, a rapid early host reaction is critical for preventing SARS-CoV-2 viremia from spreading to the lower respiratory tract and developing damaging hyperinflammation; however, the regulatory factors that control the timing and level of the host priming responses need further clarification.

As already evidenced, a dysregulated immune response is the hallmark of COVID-19. One of the contributors is the imbalanced innate immune response, termed by the upregulation of cytokine and chemokines, chemoattractants for neutrophils and monocytes in particular. Consequently, the recruitment of these cell types into infected tissues could contribute to tissue damage and elevated cytokine production, thus leading to cytokine storm. The neutralizing antibody used to play central roles in blocking viral replication and accelerating viral clearance during virus infection, which makes it a major target for vaccine development. High levels of neutralizing antibodies were induced about 10-15 days post onset and showed similar kinetics in both severe and mild patients. The positive correlation between neutralizing antibody response and disease severity indicates that, in the later phase of infection, nAb response may help no more with diseases improvement. Memory longevity and protection capability of re-infection in the convalescents need a longer term of observation and detection. The degree in which the T cell

response confers protection or induces pathogenesis through a dysregulated immune response remains uncertain. The answer to this question is essential for vaccine strategies. Longitudinal studies need to be performed for evaluating the longevity of these probably protective adaptive immune responses following natural infection or vaccination.

All these unknowns and the deeper underlying mechanisms are waiting for further elucidation by proper and detailed longitudinal studies in human trials and animal models.

Author contributions

Jincun Zhao and Nanshan Zhong carried out the concepts, design, definition of the intellectual content, and critically revised the manuscript. Airu Zhu, Zhao Chen, Yanqun Wang, Qiuhui Zeng, Jing Sun, and Zhen Zhuang carried out the search and manuscript preparation. Fang Li and Jingxian Zhao provided assistance for literature search and manuscript editing. All authors have read and approved the content of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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