REVIEW

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Cell-mediated immunity to SARS-CoV-2

Xiaolin Wang | Jingang Gui

Laboratory of Tumor Immunology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Jingang Gui, Laboratory of Tumor Immunology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China
Email: guijingang@bch.com.cn

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ABSTRACT
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses spread unscrupulously virtually every corner on the planet in a very quick speed leading to an unprecedented world pandemic of COVID-19 claiming a great many of people's life. Paramount importance has been given to the studies on the virus itself including genomic variation and viron structure, as well as cell entry pathway and tissue residence. Other than that, to learn the main characteristic of host immunity responding to SARS-CoV-2 infection is an eminent task for restraining virus and controlling disease progress. Beside antibody production in response to SARS-CoV-2 infection, host cellular immunity plays an indispensable role in impeding virus replication and expansion at various stages of COVID-19 disease. In this review, we summarized the recent knowledge regarding the aberrant regulation and dysfunction of multiple immune cells during SARS-CoV-2 infection. This includes the dysregulation of immune cell number, Th polarity, cytokine storm they implicated with, as well as cell function exhaustion after chronic virus stimulation. Notwithstanding that many obstacles remain to be overcome, studies on immunotherapy for COVID-19 treatment based on the known features of host immunity in response to SARS-CoV-2 infection offer us tangible benefits and hope for making this SARS-CoV-2 pandemic under control.

KEYWORDS
SARS-CoV-2, COVID-19, Innate immune, T-cell exhaustion, Cytokine storm, Immunotherapy

Introduction

Viral infections, especially chronic viral infections, are still a major threat to global health. Recently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rapidly spreads worldwide and causes a global health emergency. Coronavirus disease-19 (COVID-19) is an illness caused by this novel coronavirus and can present with symptoms ranging from mild or minimal respiratory symptoms to acute respiratory distress syndrome (ARDS) and related diseases.[1]

SARS-CoV-2, belonging to the large group of coronaviruses, is positive-sense single-stranded RNA (29 903 nucleotides) enveloped virus with a diameter of 60 to 140 nm.[2] The envelope is studded with homotrimers spike proteins of 8-12 nm length that are decorated with N-glycans.[3,4] Similar to other human coronaviruses, SARS-CoV-2 genome encodes four structural proteins: the spike (S), membrane (M), envelope (E) and the nucleocapsid (N) protein.[5] Mediated by the S protein, SARS-CoV-2 employs angiotensin converting enzyme 2 (ACE2) as the host cell receptor.[5,6] ACE2 highly expresses in various cell types of different human organs, including lung alveolar epithelial cells and small intestinal epithelial cells, both of which are vulnerable targets for SARS-CoV-2 transmission.[7]

Accumulated studies have already revealed the virus

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origin, the mechanisms of transmission, and the clinical features of the infection.[8] However, the SARS-CoV-2 related immune responses, particularly the cellular immune responses, remains to be explored. Multiple immune cells, including innate immune cells [(monocytes/macrophages, neutrophils, dendritic cells (DCs)] and Natural killer (NK) cells and adaptive immune cells (T cells and B cells), are proved to engage in immune responses against SRAS-CoV-2. Host immune response against SARS-CoV-2 infection varies at different disease stages with diverse workforce of activated immune cells. Since COVID-19 becomes one of the most destructive pandemics, it is paramount to understand the molecular and cellular mechanisms of SARS-CoV-2 virus infections, and most importantly, how lung and systemic host immune responses affect disease status or patient survival either positively, through down-regulating the initial viral load, or negatively, by triggering uncontrolled inflammation and inducing immune cell exhaustion.

In this review, we mainly focus on the cellular immunological features of COVID-19 and the immunotherapies with an aim to provide a deeper insight into the immune responses and immune status of this disease.

Innate immune responses and cytokine storm

Innate host response is warranted by several effector cell types, such as monocytes/macrophages, epithelial cells, neutrophils and DCs. As the first line of defense, these innate cells play a vital role in constraining the clinical symptoms and severity of COVID-19 disease. A number of studies[9-12] exploring the immune responses against SARS-CoV-2 disclosed that the immune responses are disturbed due to aberrant activation of monocytes/macrophages,[10] elevation of pro-inflammatory cytokines[11] and generation of increased proinflammatory neutrophils,[13] yet leaving the underlying initiators to be largely veiled (Figure 1).

Innate immune cells recognize pathogen-associated molecular pattern (PAMP) including viral single strand RNA (ssRNA), and intermediate replication dsRNA domains[14,15] through various classes of signaling pattern recognition receptors (PRRs).[16,17] The innate immune reaction signaling of RNA virus infection can start with the recognition of virus protein by membrane-associated Toll-like receptor 2 (TLR2) via stimulation of nuclear factor-kappaB (NF-κB) cascade in epithelial cells, monocytes and macrophages.[18] Upon viral entry, viral ssRNA enters endosomes and activates intracellular TLRs,

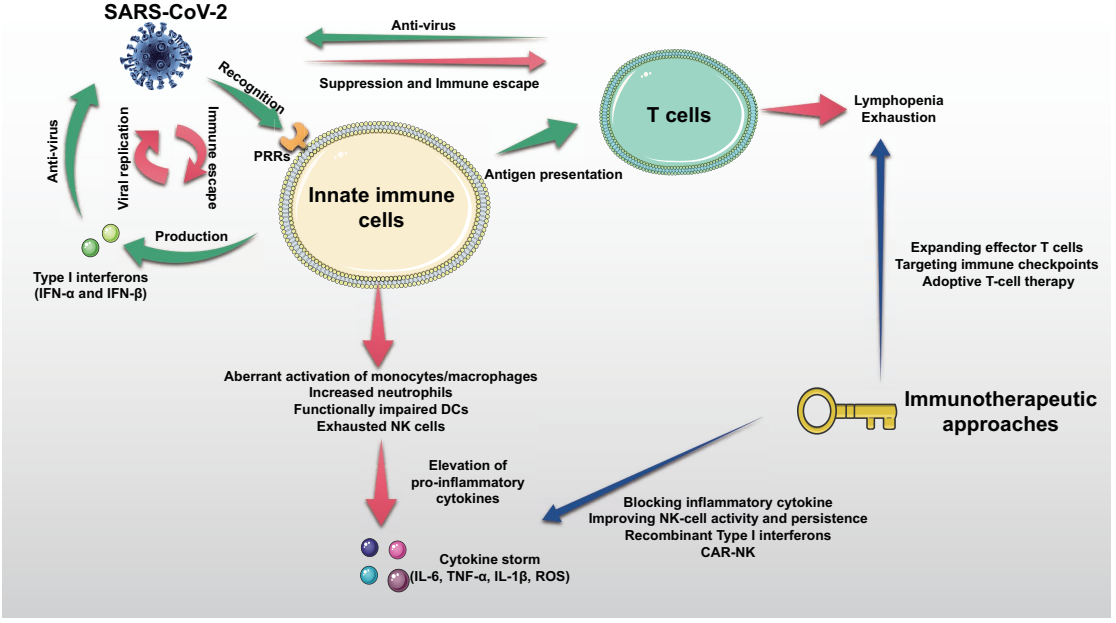

FIGURE 1 SARS-CoV-2 is recognized by innate immune cells via pattern recognition receptors (PRRs), including TLRs, RIG-I, MDA5 and NLRs. Innate immune cells are activated and produce Type I interferon (IFN) to exert antiviral function. SARS-CoV-2 antigens are processed by antigen presenting cells and presented to prime T cells, thus the activated T cells start to eliminate virus or infected cells (green arrows). However, SARS-CoV-2 can escape such innate immune recognition facilitating their replication via various strategies (possession of low content of genomic CpG islands, RNA shielding, masking of potential key antigenic epitopes, counteracting NF-κB and Type I IFN signaling). The ever-increasing SARS-CoV-2 load eventually triggers an uncontrolled immune response featuring with aberrant activation of monocytes/macrophages, generation of increased neutrophils and elevation of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) that lead to cytokine storm or cytokine release syndrome. Moreover, SARS-CoV-2 infection suppresses T-cell activity via induction of severe lymphopenia and exhaustion of T cells (red arrows). The potential immunotherapeutic approaches against COVID-19 mainly target at blocking inflammatory cytokines and restoring immune cell function, such as IL-6R neutralizing antibody, recombinant IFN-β or IL-2 treatment, anti-PD-1 monoclonal antibody and adoptive T-cell transfer (blue arrows). CAR, chimeric antigen receptor; NK, natural killer; IL, interleukin; TNF, tumor necrosis factor; ROS, reactive oxygen species.

mainly TLR7/8.[19] Elegant molecular in silico docking studies showed that the spike protein of SARS-CoV-2 is able to bind to TLR1, TLR4, and TLR6.[20] Other PRRs expressed by innate cells including retinoid inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) are also responsible for the virus recognition. Similarly to other viral infections, the expression of Type I interferons (IFN) induced by PRRs activation, such as IFN-α and IFN-β, determine the magnitude of innate immune response to SARS-CoV-2 infection (Figure 1).[21] This seems not a distinct host feature fighting against a particular virus strain since IFN-β1b and IFN-β1a were also found to be the most important Type I interferons for SARS-CoV containment.[22] These immediate responding factors subsequently induce expression of other pro-inflammatory mediators, such as cytokines, chemokines and antimicrobial peptides, all of which are essential mediators to initiate the host innate and adaptive immune response. In addition, absent in melanoma 2 (AIM2)-like receptors and NOD-like receptors (NLRs) is proven to be implicated in SARS-CoV-2 infection. Particularly, overactivation of NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome promotes IL-1β and IL-18 production exacerbating the tissue damage as well as cell death of hematopoietic stem cells.[23,24] Like other viral infections, the SARS-CoV-2 antigens are processed by specific antigen presenting cells (APCs) including macrophages and DCs.[25] The antigens are then presented by major histocompatibility complexes (MHC) or human leukocyte antigens (HLA) to specific cytotoxic T lymphocytes (CTLs).[26] It is believed that, same as SARS-CoV and MERS-CoV, the process of SARS-CoV-2 antigen mainly relies on MHC-I, with a minimum dependence on MHC-II.[27]

Coronaviruses have evolved several strategies to escape such innate immune recognition allowing their widespread replication (Figure 1). For example, possession of low content of genomic CpG islands, RNA shielding and masking of potential key antigenic epitopes are efficient strategies for evading the host immune surveillance. Knowledge arising from the studies of other coronaviruses, such as SARS-CoV, shows that SARS-CoV-2 may affect the expression of some PRRs, since SARS-CoV can craftily promote ubiquitination and thus enhance degradation of RIG-I and MDA5 RNA sensors, as well as TLR3, TLR7 and TLR8.[28,29] In addition, SARS-CoV and possibly SARS-CoV-2 can suppress innate immune responses via counteracting NF-κB and Type I IFN signaling without triggering the anti-viral machinery.[30,31]

The escape of immune recognition resulting in a subdued innate immune response facilitates the widespread viral replication during early infection. The ever-increasing SARS-CoV-2 load eventually triggers an uncontrolled immune response leading to hyperinflammation and tissue damages. Shi et al[32] described two phases of immune responses during the SARS-CoV-2 infection with the first phase installed with an immune defense-based protection, and the second phase featured with a broad inflammation.

Cytokine storm or cytokine release syndrome (CRS) is a form of aberrant systemic inflammatory response usually triggered by a variety of factors. CRS occurs when a large number of leucocytes are activated and release pro-inflammatory cytokines, which help recruit and activate more leucocytes in a positive feedback loop of hyperinflammation.[33] The hallmarks of CRS are elevated serum concentrations of pro-inflammatory cytokines including interleukin-6 (IL-6) and C-reactive protein (CRP).[34] A large number of clinical data collected from COVID-19 patients indicated that levels of pro-inflammatory cytokines such as TNF-α, IL-6, IL-8 (CXCL8), GM-CSF and G-CSF, as well as chemokines such as MCP-1, IP-10 and MIP1-α, were greatly up-regulated in patients and animal models with SARS-CoV-2 infection.[31,35-37] The presence of a mild-to-severe cytokine storm has been arguably believed as one of the most important leads for the patient death.[38,39] Evidence elucidated that cytokine storm with severe clinical manifestation was found to be closely correlated with poor therapeutic outcome in COVID-19 patients.[40]

An ample infiltration of macrophages within the area of bronchopneumonia was found in patients who died of COVID-19.[41] Moreover, macrophages expressed with ACE2 and engulfed SARS-CoV-2 nucleoprotein antigen were frequently found to infiltrate in spleen and lymph nodes of COVID-19 patients. These macrophages are believed to contribute to the excessive inflammation in COVID-19 disease via producing enormous amount of IL-6, an important player in the acute inflammation cytokine network.[42] In severe cases of COVID-19, the elevation of serum IL-6 has been observed and macrophage activation syndrome is an ascribed risk factor responsible for serious lung inflammation.[37] The high production of IL-6 accompanied with the macrophage activation syndrome, may explain the increased serum levels of CRP that are normally lacking in viral infections. A comparison of macrophage sub-phenotypes in the lung milieu in severe COVID-19 patients has revealed that the infiltrating macrophages exhibited a predominant M1 feature with pro-inflammatory effects. The persistence of M1-like macrophages in severe COVID-19 not only increases short-term mortality, but also leads to long-term complications due to hyperinflammation and delayed recovery of affected tissues.[43]

In addition to increased IL-6, augment in IL-1β and the $CD14^{+}IL\text{-}1\beta^{+}$ monocytes count with activation of NLRP3 inflammasome pathway were also described in studies of peripheral blood and tissues from severe COVID-19 cases.[44] NLRP3 inflammasome pathway promotes autocatalytic stimulation of caspase-1, which

consecutively converts immature form pro-IL-1β/IL-18 into their active forms (IL-1β/IL-18).[45,46] This catalytic cascade thus is essential for effective antiviral immune responses and however in the same time is a contributor to the hyperinflammation. Furthermore, examination of bronchoalveolar lavage fluid (BALF) samples from COVID-19 patients showed excessive up-regulation of the monocyte-attractant chemokines (such as CCL2, CCL3, CCL4, CCL7, CCL8, CCL20, CXCL6 and CXCL11) and neutrophil-attractant chemokines (CXCL1, CXCL2, CXCL8, CXCL10, CCL2 and CCL7), which implies that chemokine-guided leukocytes recruitment plays a crucial role in the development of pulmonary dysfunction.[47]

In severe COVID-19 patients the number of neutrophils is increased.[48,49] There is enough evidence to demonstrate that an increased neutrophil-to-lymphocyte ratio is an independent risk factor for a severe course of COVID-19.[13,35,50] Following SARS-CoV-2 infection, one of the first innate immune cells to infiltrate into the tissues are neutrophils, likely recruited via CXCL2 and CXCL8 produced from infected cells.[51] Platelets can induce neutrophils to produce neutrophil extracellular traps (NETs) that protect tissues from viral infection.[52] Neutrophils themselves do not clear viral particles, instead, they suppress the virus activity through releasing high levels of reactive oxygen species (ROS). Moreover, high ROS levels trigger oxidation of proteins and induce oxidative stress, which fosters pathological inflammation and unleash the cytokine storm.[10]

The investigation of DCs in COVID-19 is not enough to decode the inner linkage between their functions and SARS-CoV-2 combating. However, several direct and indirect evidence suggest that these cells might be involved in the initiation and progress of the disease, although it is unclear whether DCs might be effectors of SARS-CoV-2 activity or targets of virus infections or both. A slight increase in mature DCs in patients BALF has already been reported, suggesting that these cells participate in the immune response in lungs during SARS-CoV-2 infection.[53] MERS-CoV has been demonstrated to infect monocyte derived-DCs, rapidly inducing high expression levels of IFN-γ, IP-10, IL-12 and RANTES (regulated on activation, normal T cell expressed and secreted), and a small amount IFN-α rather than IFN-β.[54] Recent study of a cohort of 17 acute and 24 convalescent COVID-19 patients revealed a significant reduction of blood DCs with an impaired activity and an increase in the cDC/pDC ratio. Furthermore, there was also a general decrease in the pDCs subsets in the lungs of COVID-19 patients. [55,56] The specific decreased pDCs may be a result from the suppressing effects of SRAS-CoV-2 to innate immune response.

Recent COVID-19 vaccine study[57] observed the anti-spike NK cell responses in vaccinated macaques, indicating that NK cells inarguably participating in the host immune response against SARS-CoV-2-infected cells. In contrast to the elevation of macrophages or neutrophils, a significant decrease of NK cells in severe COVID-19 cases was confirmed.[58] A significant increase of NKG2A expression in COVID-19 patients was also observed. Up-regulation of NKG2A is associated with the exhaustion of NK cells at the early stage of SARS-CoV-2 infection, and therefore, is responsible for the disease exacerbation.[59] Indeed, peripheral NK cells of COVID-19 patients were found to express reduced level of CD107a, IFN-γ, and TNF-α,[60] an inauspicious sign of poor anti-virus capacity of exhausted NK cells. The function of exhaustion of NK cells is further aggravated by the hyperinflammatory milieu featured with the cytokine storm. For instance, other than neutrophilia induction, IL-6 and IL-10 have been shown to promote the expression of the exhaustion marker NKG2A on NK cells.[61]

T-cell mediated immune responses and functional exhaustion

Regarding the adaptive immune responses in COVID-19, both humoral and cellular immune responses to SARS-CoV-2 are indispensable for anti-infection activities. Humoral immune responses to SARS-CoV-2, discussed extensively in recent studies, are mediated by antibodies directly targeting viral surface glycoproteins, primarily the spike glycoprotein and the nucleocapsid protein. Various subtypes of B lymphocytes are reported being involved in the humoral immune response against coronavirus infections.[62] Limited data on cellular immunity against SARS-CoV-2 reveal that T cells mediate antiviral immune responses through interacting with virus-infected cells directly, or regulating the humoral immune componets indirectly.

As mentioned above, the infection of SARS-CoV-2 triggers innate immune cells and drives an inflammatory cascade encompassing Type I IFNs that not only inhibits virus replication but also facilitates the presentation of viral epitopes by APCs for priming of T and B cells (Figure 1).

It is presumed that SARS-CoV-2 induces a similar IFN-γ-producing Th1 type immune response as other viral infections.[63] Furthermore, $CD4^+$ T cells specific for the SARS-CoV-2 spike protein have been identified in acute infection and found to skew to a Th1 cell cytokine profile.[64] Patients with mild disease may have a normal Th2 cell response,[65] yet what role Th2 response plays in severe COVID-19 is unclear. Since Th2 cells are one of important players in other lung diseases, their action in COVID-19 possibly would emerge along with further studies. Recent studies have described a strong $CCR6^+CD4^+$ T cell signature in severe COVID-19, which indicates a potential role for Th17 cell-mediated immunopathology.[35,66] The possible role of IL-17 and related altered cytokines are highlighted in SARS-CoV-2 infection. IL-17 produced

by Th17 cells mediates the activation of monocytes/macrophages, DCs and neutrophils and enhances the production of cytokines (IL-1, IL-6, IL-8, IL-21, TNF-α, and MCP-1) from these cells,[9,67] thus contributing to the cytokine storm. The increased Th17 cells may be caused by elevated IL-6, a factor important for the development of Th17 cells. In addition, regulatory T cells (Treg) increase during the progression from mild to severe condition but then decline during the progression to critical condition.[68] It has been shown that in some COVID-19 cases, without disturbing the total circulating T follicular helper cells (cTfh) cell number, the ratio of $ICOS^+CD38^+$ activated cTfh cells increased.[69] Severe COVID-19 also linked with the increased number of circulating plasmablasts.[70]

Regarding $CD8^+$ T cells, data from patients who have recovered from SARS-CoV-2 infection suggested that a prototypical antiviral $CD8^+$ T cell response was activated during SARS-CoV-2 infection.[71,72] $CD8^+$ T cells are primed to identify viral epitopes bound to MHC-I of virus-infected cells, eliminate the virus replication, and maintain immunological memory. Indeed, strong effector and memory $CD8^+$ T-cell immunity is a hallmark of many common human viral infections. Like $CD4^+$ T cells, SARS-CoV-2-specific $CD8^+$ T cells skew to Th1 polarity by producing IFN-γ and TNF-α.[73] Increased numbers of $CD38^+HLA\text{-}DR^+$ activated $CD8^+$ T cells were observed in many, but not all, patients.[70,71] Some studies suggested that $CD8^+$ T cells might have a hyperactivation signature presenting with high levels of NK cell-related activating markers and increased cytotoxicity.[65] SARS-CoV-2-specific T cells can express perforin 1 and granzymes upon *in vitro* restimulation with viral antigens. Worth to be noted, some studies showed that $CD8^+$ T cells isolated from patients with severe COVID-19 were featured with reduced cytokine production upon stimulation.[59] It is possible that different study timing, varying definitions of mild and severe disease, and other factors may cause the conflicting results.

Other than classic adaptive $CD4^+$ and $CD8^+$ T cells, the T-cell compartment comprises several lineages of cells endowed with both innate and adaptive properties referred as unconventional T cells.[74] These include mucosa-associated invariant T (MAIT), γδT, and invariant natural killer T (iNKT) cells. With a decreased proportion in circulation, unconventional T cells were highly activated in lung of COVID-19 patients, endorsing their potential contribution to the hyperinflammation.[75]

One prominent feature of SARS-CoV-2 infection is lymphopenia (Figure 1).[12,40] Lymphopenia is associated with severe diseases but is reversed when patients recover.[72,76] The count of $CD8^+$ T cells was shown to decrease during SARS-CoV-2 infection, and in severe cases, memory $CD4^+$ T cells and Treg cells count were remarkably reduced.[58] In addition, T cell lymphopenia has been shown to correlate with disease severity, suggesting a role for these cells in the pathophysiological progression of severe COVID-19.[35,72] In severe disease, lymphopenia may be associated with high levels of IL-6, IL-10 or TNF-α,[77] through which a suppression of T-cell populations is achieved by direct cytokine impact[78] and/or indirect effects via other cell types, such as DCs and neutrophils.[13] Hyperactivation of T cells or induction of expression of pro-apoptotic molecules, such as FAS, TRAIL or caspase-3,[69,79] could also be a culprit of T cell depletion. During SARS-CoV-2 infection, a reduction in the quantity and quality of $CD4^+$ T cells leads to an attenuated activation of B lymphocytes, subsequently, being incapable of producing sufficient virus-specific neutralizing antibodies for the clearance of virus from infected organs.[80]

As mentioned above, in severe disease cases, both the proportion and activity of $CD4^+$ and $CD8^+$ T cells are impeded, although T cells are elevated in patients with mild COVID-19, creating a robust antiviral immune response.[81] Moreover, SARS-CoV-2, similarly to other coronaviruses, restrains antigen presentation via down-regulating MHC-I and II molecules, and as a result, T-cell mediated immune responses are dampened.[59] As a negative regulatory signal for the activation and proliferation of T cells, the immune checkpoint pathway is involved in the immune escape of many viruses. Many chronic viral infections result in T-cell exhaustion, which is one of the major reasons preventing host from effective infection elimination.[82] Indeed, T-cell exhaustion in severe COVID-19 cases was proven to contribute greatly to the impaired immune responses.

Similar to the increased NKG2A expression in NK cells, it has been revealed that the terminally differentiated T cells or possibly exhausted T cells in severe disease express increased levels of the inhibitory receptors including PD-1, TIM-3, LAG3, CTLA-4, NKG2A and CD39 (Figure 1).[59,60] The frequency of $CD8^+PD\text{-}1^+CTLA\text{-}4^+TIGIT^+$ T cells in the blood circulation of severe COVID-19 patients was reported higher than that of mild cases.[60] Along with the elevated expression of inhibitory molecules, $CD8^+$ T cells in COVID-19 patients were found to have diminished ability for degranulation (decreased CD107a externalization) and produce much lower levels of IL-2, IFN-γ, and granzyme B as compared to healthy donors.[59,60] Moreover, high proportions of both activated $CD4^+HLA\text{-}DR^+CD38^+$ T cells and $CD4^+PD\text{-}1^+CD57^+$ exhausted T cells were detected in COVID-19 patients, compared with healthy controls.[83] It was also demonstrated that $CD4^+$ T cells characteristic of low levels of IFN-γ, IL-2 and TNF-α were presented with a higher ratio in severe COVID-19 patients, compared with healthy controls and mild patients.[60] Likewise, frequency of PD-1-expressing unconventional T cells that produce less IFN-γ increased in COVID-19 patients.[75] Nevertheless, it is very likely that

the antiviral activity of T cells could be restored in light of the observation that the expression of negative regulator, NKG2A, returns to its basal level in recovered patients.[59]

From another perspective, the expression of these inhibitory receptors could be a collateral event in response to recent T-cell activation, and it is not yet clear whether T cells in patients with COVID-19 are completely exhausted or just highly activated. Possibly, during the acute infection, innate immune cells are triggered by SARS-CoV-2, thus priming T cells to engage antiviral function and maintain immune balance, and the expression of inhibitory receptors is merely a result from T-cell activation. In contrast, in a scenario of long-term chronic SARS-CoV-2 infection or severe disease condition, elevated expression of inhibitory receptors accumulate to cross the turning point for T-cell exhaustion and initiate the termination of T-cell function.

Taken together, these findings indicate a strong immunosuppressive character of host adaptive immunity in response to SARS-CoV-2 infection. Reversing T-cell exhaustion could be a promising approach for the immunotheraty of COVID-19. In the same time, a devastating cytokine storm must be avoided during which the immune checkpoints are blocked and T-cell activation are rebooted.

Cellular immunity based immunotherapy of COVID-19

Various immunotherapies against COVID-19 has been extensively investigated with many ongoing clinical trials. These strategies include enhancement of cell-mediated antiviral responses directly or indirectly, blockade of pro-inflammatory cytokines, and restoration of compromised immune cell function (Figure 1 and Table 1).

During CRS of COVID-19, IL-6 is an important member of the cytokine network and plays a key role in acute inflammation. Blockade of IL-6 signal transduction has become an important therapeutic approach in the severe COVID-19 cases. Tocilizumab, a highly effective IL-6 signal blocker, is a recombinant human monoclonal antibody against soluble and membrane-bound IL-6 receptor (IL-6R). A recent study from China reported an auspicious response in 15 out of 20 (75%) patients treated with tocilizumab for 5 days.[84] An Italy-based study using siltuximab (a human-murine chimeric monoclonal antibody against IL-6) saw a beneficial effect in 7 out of 21 (33%) COVID-19 patients.[85] Other pro-inflammatory cytokines, such as IL-1β and TNF-α, have been used as the potential target for COVID-19 treatment. Anakinra, a recombinant IL-1 receptor antagonist, was demonstrated to associate with serum CRP reduction and progressive improvements in respiratory function in 21 out of 29 (72%) COVID-19 patients.[86] More clinical trials have been planned to evaluate the safety and efficacy of these anti-inflammatory treatments.

Moreover, due to the aforementioned Th17 immune responses in cytokine storm, targeting Th17 responses could offer another therapeutic strategy for treating severe COVID-19 patients. Blocking Th17 responses with IL-17

TABLE 1 Therapeutic strategies against COVID-19 based on modulation of cellular immune responses

Therapeutic strategy	Pathway or molecular target	Potential benefits	Reference or clinical trial numbers
Anti-IL-6	Monoclonal antibodies against IL-6R (tocilizumab) or IL-6 (siltuximab)	Blocking IL-6 signaling pathway to prevent virus-related cytokine storm and reduce symptoms of severe COVID-19	84 85
Anti-IL-1β	Recombinant IL-1 receptor antagonist (anakinra)	Blocking IL-1β related proinflammatory responses	86
JAK2 inhibitor	JAK2 specific inhibitor (fedratinib)	Inhibiting JAK2-mediated cytokine release	87
IFN-β therapy	Recombinant IFN-β1b treatment	Activating interferon pathway to eliminate virus	88
IL-2 or IL-7 therapy	Recombinant IL-2 or IL-7 treatment	Restoring T cell count and reversing lymphopenia, expanding Tregs to constrain excessive inflammation	NCT04407689, NCT04379076, and NCT04426201
Anti-PD-1	Monoclonal antibodies against PD-1 (pembrolizumab or nivolumab)	Reversing T or NK cell exhaustion	NCT04268537, NCT04333914, NCT04356508, and NCT04413838
Adoptive T cell transfer	N/A	Improving specific antiviral T cell responses	NCT04351659 and NCT04401410
Adoptive NK cell transfer	N/A	Improving antiviral NK cell responses	NCT04344548 and NCT04365101
CAR-NK Cells	N/A	Facilitate the elimination of SARS-CoV-2 virions and infected cells by NKG2D-ACE2 CAR-NK cells	NCT04324996

COVID-19, coronavirus disease-19; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL, interleukin; IFN, interferon; NK, natural killer; JAK2, Janus Kinase 2; Tregs, regulatory T cells ; PD-1, programmed cell death protein 1; CAR, chimeric antigen receptor; NKG2D, natural killer group 2, member D; ACE2, angiotensin converting enzyme 2.

neutralizing antibody, antibodies against IL-17R and/or IL-12/23p40, as well as small molecule drugs such as Janus kinase 2 (JAK2)-specific inhibitor, could provide an effective avenue to mitigate cytokine storm in severe COVID-19 cases.[87]

Type I IFN signal pathways make great contribution to efficient antiviral responses, whereas they are possibly impaired by SARS-CoV-2 in COVID-19 patients. Therefore, eliciting the Type I IFN responses is a very promising therapeutic strategy. Numerous clinical trials using recombinant human type I IFNs to treat COVID-19 patients are currently under investigation. A recently published phase II study (NCT04276688)[88] showed that complementing lopinavir-ritonavir and ribavirin with subcutaneous IFN-β-1b in mild-to-moderate COVID-19 patients was safe without serious adverse events and highly effective. This treatment perceives a prominent mitigation of symptoms, significant reduced length of hospital stay and time to diminish viral load. However, as a side effect that is not ignorable, Type I IFN therapy possesses a risk of excessive activation of pro-inflammatory responses.

In addition to IFN cytokine therapy, interleukin cytokine therapy exhibits a promising effectiveness in promoting T and NK cell responses in COVID-19 patients. As instances, both IL-2 and IL-7 induce the proliferation of naive and memory T cells and increase the circulating pool[89, 90] and they may exert positive effects in resolving lymphopenia of COVID-19 patients. Clinical trials to evaluate the efficacy of recombinant IL-7 to restore lymphocyte counts in COVID-19 patients have been registered (NCT04407689, NCT04379076 and NCT04426201). The administration of low-dose recombinant IL-2 in COVID-19 patients has been proposed as an alternative therapeutic strategy to resolve lymphopenia through expanding effector T cells, and in the same time controlling CRS and excessive inflammation by expanding and activating Tregs (NCT04357444).[91] Furthermore, since IL-15 improves the activity and persistence of NK cells,[92] the safety and efficacy of IL-15-based therapy against COVID-19 is worthy to be explored.

We have discussed the poor antiviral immune response mediated by exhausted T and NK cells with increased expression of inhibitory immune checkpoints in COVID-19 patients. Logically, targeting immune checkpoints could have therapeutic potentials in COVID-19 patients. Up to date, several studies have been conducted to evaluate the effect of immune checkpoint inhibitors on disease symptoms and clinical outcomes in COVID-19 patients. Targeting PD-1 and possibly other immune checkpoints in COVID-19 patients could reasonably be beneficial with regard to releasing T cells from exhaustion, and inducing stronger T cell proliferation and more cytotoxic $CD8^+$ T cells.[93] Four clinical trials have been conducted to assess the safety and therapeutic efficacy of anti-PD-1 monoclonal antibody (pembrolizumab or nivolumab) in patients with COVID-19 (NCT04268537, NCT04333914, NCT04356508 and NCT04413838).[91] However, findings from some pre-clinical models suggested excessive inflammation and tissue damage could be induced by PD-1 blocking.[94] Therefore, it might be ideal to combine anti-PD-1 therapy with other treatments, such as anti-IL-6 receptor therapy, to reduce the treatment-related cytokine storm. Other markedly up-regulated immune checkpoints in COVID-19, such as TIM-3 or NKG2A, are also potential targets for immunotherapy. Blocking NKG2A *in vitro* with NKG2A monoclonal antibodies was proven to lead improved NK cytotoxicity[95] and anti-NKG2A therapy is worthy to investigate further with an aim to obtain a higher NK response against SARS-CoV-2 virus.

The applications of adoptive transfer of T or NK cell as a treatment in various severe disease conditions including infection and tumor suggest that it could likewise be a potential therapeutic approach for COVID-19 treatment. Autologous or allogeneic viral-specific T cells can be expanded *in vitro* and infused to restore effective antiviral immunity, and have shown efficacy in controlling various viral infections.[96] SARS-CoV-2-specific T cells can be isolated from circulation of convalescent donors and expanded using SARS-CoV-2-derived peptides. A clinical trial based on adoptive T-cell therapy for COVID-19 is now being carried out (NCT04351659) and another clinical trial is adopting an innovative approach of utilizing SARS-CoV-2 specific T cells from recovered patients to treat COVID-19 patients with high risk of respiratory failure (NCT04401410).[91] Moreover, adoptive NK cell therapies are also conducted to test the safety and efficiency. In these settings, adoptive transfer of isolated NK cells stimulated with IL-2 and IL-15 *in vitro* (NCT04344548), or adoptive transfer of placental $CD34^+$ cells derived NK cells (NCT04365101) are tested in different clinical trials. Genetically modified NK cells are also being investigated for efficacy against COVID-19. A phase I/II study in early stage COVID-19 patients treated with CAR-NK cell therapy is currently being tested using NK cells derived from human umbilical cord blood expressing NKG2D and ACE2 CARs (NCT04324996). It is hypothesized that expressing ACE2 CAR on NK cells will facilitate the elimination of SARS-CoV-2 virions and infected cells by binding the viral spike proteins.[97] Similarly, CAR-T cell therapy is also an approach worth to try though the related trails have not been carried out. However, challenges associated with adoptive immune cell transfer, including inadequate treatment efficacy and treatment-related toxicities, have limited their use in COVID-19 patients. Further investigation should put more emphasis on how to get over these challenges inherently attached to these otherwise ideal approaches for COVID-19 treatment.

Conclusion

In conclusion, the topics discussed in this review aim at providing most recent knowledge on the aberrant cell-mediated immunity in host against SARS-CoV-2 and potential immunotherapies for COVID-19. Questions should be asked like: which immune cell response plays a major role in different stages of SARS-CoV-2 infection; how does SARS-CoV-2 escape and suppress immune responses in a deeper molecular basis; what pathological scenario during SARS-CoV-2 infection, a mode of immune cell exhaustion rather than activation would be established. Up to date, great developments in COVID-19 immunotherapies have been achieved. However, researchers should still pay much attention to solve the main problem of immunotherapy in COVID-19, the application of different treatments according to the infectious stages and severity, to increase efficiency and to reduce side effects, such as excessive activation or cytokine storm.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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