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IL-15 immunotherapy is a viable strategy for COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pulmonary inflammatory disease induced by a newly recognized coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection was detected for the first time in the city of Wuhan in China and spread all over the world at the beginning of 2020. Several millions of people have been infected with SARS-CoV-2, and almost 382,867 human deaths worldwide have been reported so far. Notably, there has been no specific, clinically approved vaccine or anti-viral treatment strategy for COVID-19. Herein, we review COVID-19, the viral replication, and its effect on promoting pulmonary fibro-inflammation via immune cell-mediated cytokine storms in humans. Several clinical trials are currently ongoing for anti-viral drugs, vaccines, and neutralizing antibodies against COVID-19. Viral clearance is the result of effective innate and adaptive immune responses. The pivotal role of interleukin (IL)-15 in viral clearance involves maintaining the balance of induced inflammatory cytokines and the homeostatic responses of natural killer and $CD8^+$ T cells. This review presents supporting evidence of the impact of IL-15 immunotherapy on COVID-19.

1. Introduction

Previously known four different coronaviruses (CoV), namely HKU1, NL63, 229E, and OC43, can induce mild respiratory diseases. The first outbreak of coronavirus was reported to have originated in bats and crossed over to humans via the intermediary host palm civet cats in the province of Guangdong in China in 2002 [1]. In 2012, coronavirus was reported again in the Middle East that originated in bats in Saudi Arabia with dromedary camels as the intermediate host, and it was named Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. This virus also caused acute respiratory disease. The third outbreak caused by the worst type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported to originate from the city of Wuhan in China in Jan 2020 and spread worldwide to cause the coronavirus disease (COVID-19). SARS-CoV-2 is a fast-spreading virus between humans by close contact, which has infected approximately 6.4 million people and caused almost 382,867 deaths as of June 04, 2020. The current means of stopping viral transmission is only by restricting social contact. SARS-CoV-2 is an enveloped positive-sense RNA virus of 60 nm–140 nm in diameter with spike-like projections identified by electron microscopy [3]. Herein, this review highlights the biology of SARS-CoV-2 and possible novel immunotherapy with interleukin (IL)-15 for COVID-19 infection in humans.

2. IL-15 is required for the maintenance of innate immunity and promotes viral clearance

IL-15 is a critical immunoregulatory cytokine with anti-viral properties [4]. IL-15 is expressed by myeloid cells to aid in T cell responses, activate natural killer (NK) cells, and modulate inflammation [5]. In lymphocytes, activated IL-15 binds to the IL-2/15Rβγ heterodimer and induces signal transduction via phosphorylation of Janus-associated kinases (JAK) and signal transducer and activator of transcription (STAT) proteins. JAK1 activation phosphorylates STAT3 via the β chain, whereas JAK3/STAT5 activation occurs via the γ chain. The STAT3/STAT5 form heterodimers upon phosphorylation [6,7] and translocate to the nucleus to activate Bcl-2, c-Myc, c-Fos, c-Jun and NF-κB [8–11]. Akt is activated via a phosphatidylinositol 3-kinase (PI3K)-dependent pathway. Shc is an adaptor protein that binds to a phosphotyrosine residue on the IL-2/15Rβ heterodimer and activates Grb2, which then activates Akt, resulting in an increase in cell proliferation and/or survival [12,13]. IL-15 trans-presentation to IL-2/15Rβγ and Shc-mediated activation of Grb2 lead to the formation of Grb2-SOS complex that further activates the Ras-Raf pathway by facilitating the removal of GDP from a member of the Ras subfamily, activating the

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mitogen-activated protein kinase (MAPK) pathway for cellular proliferation [14–16].] IL-15 deficiency has been previously shown to promote airway resistance in mice, whereas IL-15 inhibits pro-inflammatory cytokines, reduces goblet cell hyperplasia, and regulates allergen-induced airway obstruction in mice by inducing Interferon (IFN)-γ and IL-10-producing regulatory $CD4^+CD25^+Foxp3^+$ T cells [17]. In another study, rIL-15 treatment has been showed to further protect mice from chronic fibro-inflammation via the induction of IFN-γ-responsive invariant NK T cells [18]. Human IL-15 cytokine integration into the genome of the Wyeth strain of vaccinia induces powerful immunogenicity in mice [19]. IL-15 enhances the activity of NK cells, whereas blocking IL-15 delays NK cell entry into mouse lung airways infected with influenza, resulting in dysregulated control of viral replication. IL-15 regulates innate and adaptive responses to influenza infection by mobilizing NK cells to control early viral replication. Depletion of $NK1.1^+$ cells is associated with a decrease in the migration of influenza-specific $CD8^+$ T cells at the site of infection [20]. IL-15 may be a novel therapeutic molecule, and we have previously showed that IL-15-responsive RORγ + T regulatory cells are expressed in IL-15-overexpressing allergen-challenged mice to restrict pulmonary fibrosis [21]. A clinical trial is under way using intravenous infusions of Natural Killer Group 2D (NKG2D)-Angiotensin-converting enzyme 2 (ACE2) chimeric antigen receptor (CAR)-NK cells with an IL-15 superagonist and Granulocyte-macrophage colony-stimulating factor (GM-CSF) neutralizing single-chain variable fragments for the treatment of COVID-19. This therapy aims to target SARS-CoV-2 and Natural killer group 2D ligand (NKG2DL) with ACE2 and NKG2D on the surface of infected cells for effective removal of SARS-CoV-2 virus particles (https://clinicaltrials.gov/ct2/show/NCT04324996). An earlier report has shown that plasma IL-15 levels are increased in MERS-CoV infected patients, which demonstrates that IL-15 induced NK and $CD8^+$ T cell responses are effective in eliminating virus-infected cells [22]. Further, Wyeth/IL-15/5Flu and Wyeth/mutIL-15/5Flu vaccines have been reported to promote defense against clade 2.2 H5N1 infection [23]. These data demonstrate that induced IL-15 improves both humoral and cellular responses against respective viral antigens and protects infected individuals. Most recent report indicates that IFN-α2b with or without arbidol reduces virus load in the upper respiratory tract [24]. Since, IL-15 is critical for the development, survival and function of several innate cells including NK cells that regulates IFN-α/β; we hope that the innate immune responses associated with IL-15 overexpression may also be critical in the treatment of SARS-CoV-2 infection. Therefore, a double-blind clinical trial with IL-15 immunotherapy is warranted to establish the critical therapeutic effects of IL-15-induced innate immune responses for patients infected with COVID-19.

3. Epidemiology of COVID-19

Coronavirus belongs to the family Coronaviridae and the order of Nidovirales, which is a type of enveloped positive-sense RNA viruses distributed in mammals. Earlier outbreaks of coronavirus diseases that led to severe threats to human health at the beginning of the 21st century were caused by the severe acute respiratory syndrome (SARS)-CoV and the MERS-CoV [25]. The natural reservoir for these viruses includes wild animals like bats, from which the virus may be transmitted to a secondary host and humans [26]. SARS-CoV-2 is 96 % similar to bat coronaviruses at the whole genome level [27]. Zhang et al. determined the probable pangolin origin of SARS-CoV-2, which was 91.02 % similar to SARS-CoV-2 at the genome level [28]. COVID-19, an inflammatory viral disease caused by the novel coronavirus SARS-CoV-2, is a deadly disease emerged in December 2019 in Wuhan city, Hubei province of China. A recent study identified the novel coronavirus by deep sequencing analysis of isolated human airway epithelial cells from patients with pneumonia, which was later named SARS-CoV-2 [29]. The initial events of virus spread was associated with animal-to-animal contact, and subsequent spread to humans was linked to the Huanan seafood market [30]. It has affected several countries across the globe with a wide community spread and high mortality. There are numerous clinical trials under way in developing potent vaccines and potential anti-viral and neutralizing therapies for COVID-19 [31]. The mortality of COVID-19 aggravates in patients with co-morbid conditions like hypertension, diabetes, obesity, cancer, chronic respiratory disease, chronic kidney disease, and liver diseases. Besides chronic obstructive pulmonary disease, a history of asthma worsens disease severity and increases mortality rate in COVID-19 patients [32,33]. The expression of ACE2 receptor is upregulated in the lung tissues of tobacco smokers, suggesting that smoking is a critical risk factor for viral infections [34]. Current data indicate that older adults and people of any age with co-morbidities might be at an elevated risk of severe illness and mortality from COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html).

SARS-CoV-2 infected patient's manifest dry cough, itchy throat, and increased body temperature at the onset. As the disease progresses, most patients exhibit pneumonia with dyspnea, pulmonary inflammation, myalgia, fatigue, and reduced leukocyte counts. SARS-CoV-2 infected patients can be identified by radiological evaluation of pneumonia and laboratory detection of viral infection. Recent report indicates that the infection of SARS-CoV-2 not only damage the lung, but also affect multiple organs in virus infected patients [35]. Males have been shown to exhibit higher rate of SARS-CoV-2 infection and mortality than females, which may be attributed to the female X chromosome that is associated with less viral loads, lower levels of IL-6 and inflammation, higher levels of $CD4^+$ T cells, antibodies, and immune cells, along with the activation of Toll-like receptor 7 (TLR7) and IFN in females [36]. A study with 38 pregnant women with COVID-19 shows no evidence of intrauterine or transplacental transmission of SARS-CoV-2 from infected pregnant women to their fetuses [37], which still needs to be verified in future research. SARS-CoV-2 also infects children, who are less susceptible to the infection with milder disease course, better prognosis, and a lower mortality rate than those in adults [38,39]. There has been an increasing concern over pediatric multisystem inflammatory syndrome that requires intensive care to be potentially associated with COVID-19, and the commonly reported symptoms include fever, abdominal pain, vomiting, diarrhea, rashes and cardiac inflammation. The blood work is consistent with severe pediatric COVID-19 cases, with overlapping features of toxic shock syndrome and atypical Kawasaki disease [40]. Mutation hotspots have been identified by sequencing analysis of the spike protein of SARS-CoV-2 that is involved in viral virulence [41]. As of June 04, 2020, 6.4 million cases of COVID-19 have been reported globally with 382,867 deaths. The worldwide spread of COVID-19 is presented in the heat map modified from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200517-covid-19-sitrep-118.pdf?sfvrsn=21c0dafe_8 (Fig. 1).

4. COVID-19 entry and replication

The human SARS-CoV-2 genome encompasses the 5′-untranslated region (5′-UTR), open reading frame (ORF) 1a/b encoding non-structural proteins that aid in replication, ORFs encoding structural proteins including spike (S), envelop (E), membrane (M), and nucleocapsid (N) proteins, ORFs 3, 6, 7a, 7b, 8 and 9b encoding accessory proteins, and the 3′-UTR. The M and E proteins help with viral assembly, and the N protein is critical for RNA synthesis as shown in Fig. 2 A–C. The S protein plays a vital role in viral entry into host cells by biding to the ACE2 receptor. Membrane fusion of SARS-CoV-2 is primed by proteases cathepsin L and Transmembrane Serine Protease 2 (TMPRSS2) via cleavage at the S1/S2 and the S2 sites [42]. The conformation change in the S protein facilitates the fusion of viral envelope with the cell membrane through the endosomal pathway, followed by RNA release from SARS-CoV-2 into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and pp1ab, which are cleaved by viral

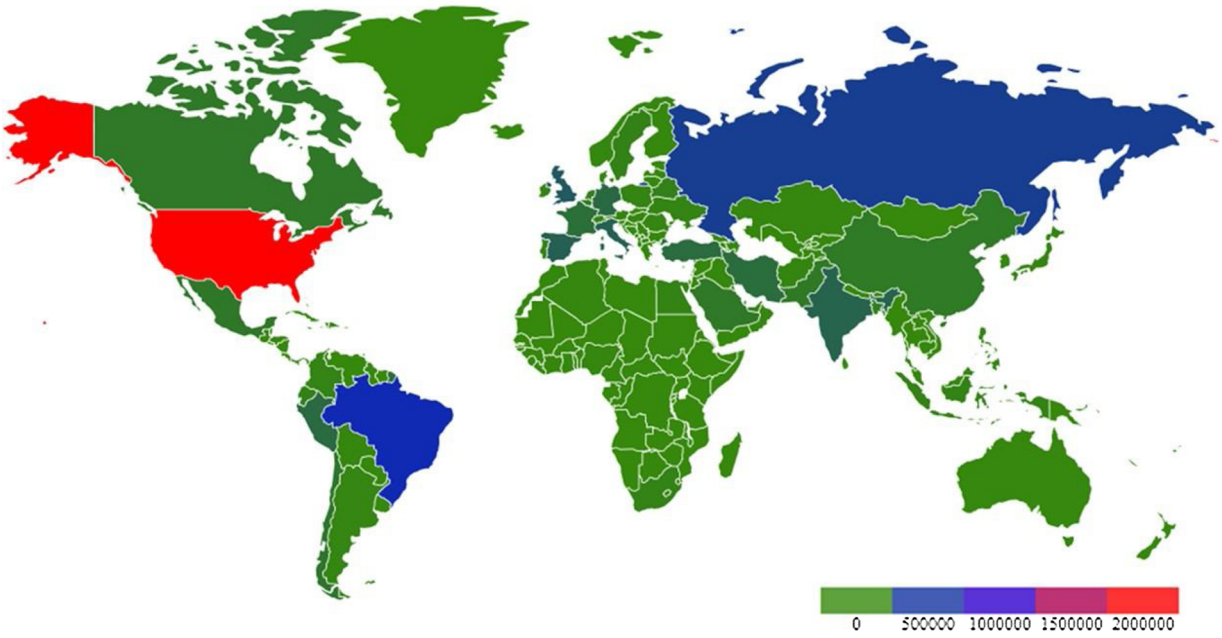

Fig. 1. Global cases of COVID-19 as of 06/04/2020.
(https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200604-covid-19-sitrep-136.pdf?sfvrsn=fd36550b_2)

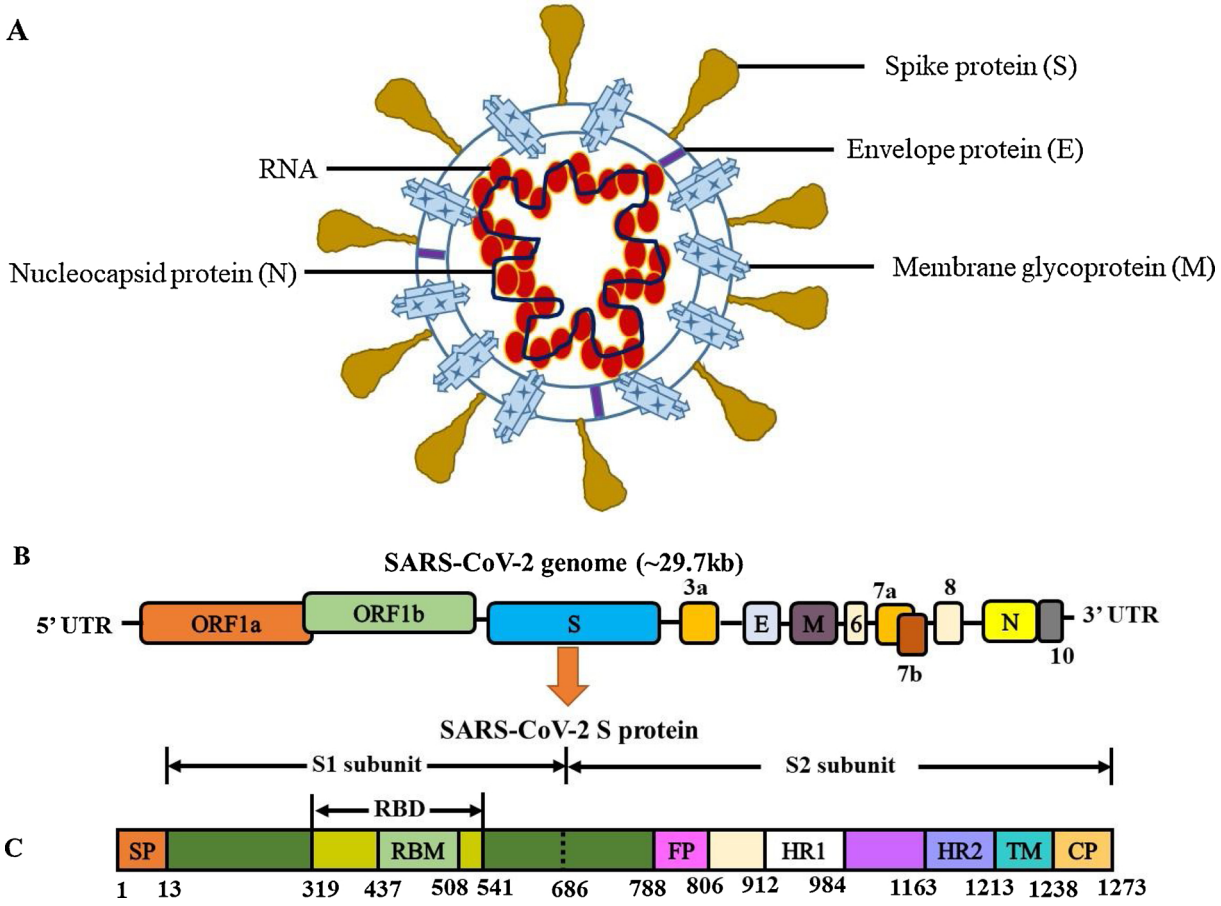

Fig. 2. Schematic of the virion, the genome and the spike protein of SARS-CoV-2 that causes COVID-19, a human respiratory syndrome. A) The viral surface, spike, envelope, and membrane proteins are embedded in a lipid bilayer and the single-stranded positive-sense viral RNA is associated with the nucleocapsid protein. The SARS-CoV-2 genome encompasses the 5′-untranslated region (5′-UTR), open reading frame (ORF) 1a/b encoding non-structural proteins for replication, ORFs encoding structural proteins including spike, envelop, membrane, and nucleocapsid proteins, ORFs encoding accessory proteins such as ORF 3a, 6, 7a, 7b, 8 and 10, and the 3′-UTR. B) Genome organization of SARS-CoV-2. C) SARS-CoV-2 spike glycoprotein. The S1/S2 cleavage sites are indicated by dotted lines. In the S protein, the S1 subunit is comprised of signal peptide (SP), receptor (ACE2)-binding motif (RBM), and receptor-binding domain (RBD); the S2 subunit is comprised of fusion peptide (FP), heptad repeat (HR), transmembrane domain (TM), and cytoplasm domain (CP).

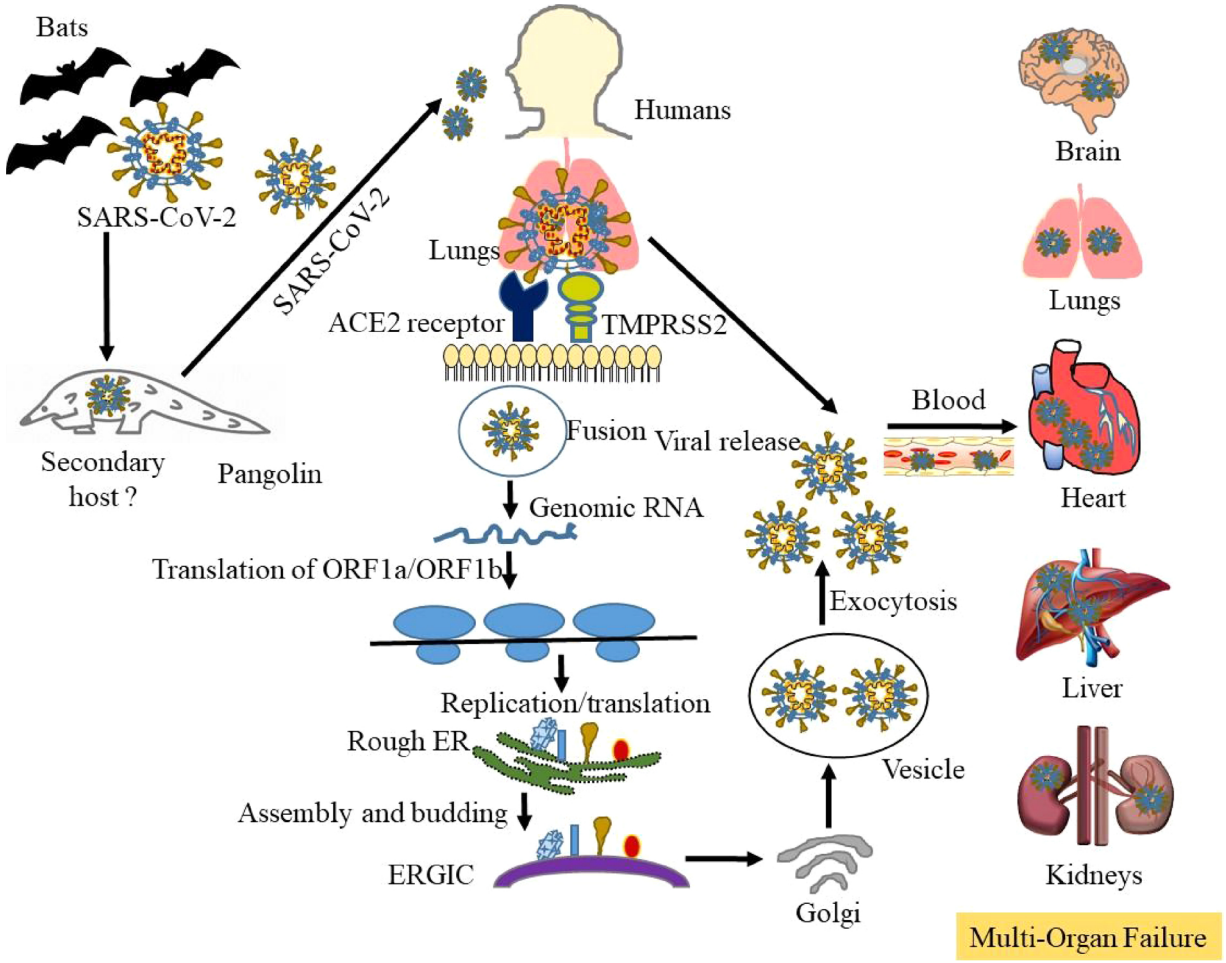

Fig. 3. Transmission of SARS-CoV-2, replication in humans, and induction of pulmonary fibro-inflammation and organ failure. SARS-CoV-2 that causes COVID-19 may originate from the primary host bats or unknown secondary hosts and cross the species barrier to humans. The spike protein on SARS-CoV-2 binds to the cell surface receptor ACE2 and the enzyme TMPRSS2, which aid the virion entry. The virion releases its RNA, part of which is translated into proteins. Proteins and the RNA are assembled into a new virion in the Golgi and released. Exposure to SARS-CoV-2 induces immune cell infiltration that promotes inflammatory cytokine storms and multi-organ failure via the acute respiratory distress syndrome.

proteinases. Subgenomic mRNAs produced by polymerases are translated into relevant viral proteins by discontinuous transcription, assembled into virions in the ER and Golgi, transported via vesicles, and released out of the host cell [43]. The released SARS-CoV-2 infects not only the lungs, but key organs like the brain, heart, intestine, kidney, and liver through ACE2-mediated pathways. Its pathogenesis involves induced cytokine storms, immune cell infiltration, and the depletion of T cells. These pathological changes lead to acute respiratory distress syndrome (ARDS), hypoxia with myocardial, hepatic, renal, and central nervous system injuries, and may contribute to organ failure and increased mortality as depicted in Fig. 3 [44,45]. COVID-19 is also detected in asymptomatic carriers by CT imaging and RT-PCR tests, and the wide spread of asymptomatic transmission makes it challenging to prevent COVID-19 infections [46,47].

5. Immune cell infiltration and cytokine storms with SARS-CoV-2 infection

Immune cell infiltration and cytokine storms have been reported in patients with SARS-CoV-2 infection. The levels of inflammatory cells including eosinophils were low at disease onset but returned to normal before patients are discharged, indicating that COVID-19 patients may benefit from continued use of lopinavir, a strategy that needs to be verified in future studies [48]. The neutrophil to lymphocyte ratio (NLR) is a marker for the overall inflammatory status of patients; increased NLR is a risk factor in various diseases and is reported to be increased in COVID-19 patients, suggesting that it can be an independent risk factor for mortality in SARS-CoV-2 infected hospitalized patients [49]. Necropsy of two patients infected with SARS-CoV-2 showed pulmonary hemorrhage, epithelial injury, spherical hyaline degeneration bodies with macrophage infiltration and fibrosis, and desquamated alveolar cells in the lung. Immunohistology identification has also confirmed the expression of chemokines and inflammatory cytokines IL-6, IL-10, tumor necrosis factor (TNF)-α, programmed death-ligand (PDL)-1, and $CD68^+$ macrophages. Incubation of purified and Fc-tagged spike proteins of SARS-CoV-2 that have receptor binding domains to enter white blood cells showed evidence of the S protein interacting with CD68-expressing monocytes or macrophages but not with T or B lymphocytes. The expression of ACE2 was also observed on macrophages. This study demonstrates the critical role of macrophages as the host cells for SARS-CoV-2 and the potential driver of cytokine storms [50].

6. T cell immunity in viral infections

T cell cytotoxic subsets and NK cells play an important role in viral clearance; exhaustion of such cells increases disease severity. NKG2A is an inhibitory receptor associated with NK cells to restrict viral replication [51]. A recent study showed a decrease in NK cells and $CD8^+$ T cells with an increased expression of NKG2A, whereas recovering

Table 1
Pharmacology of selected COVID-19 treatments under investigation. Resources: () FDA, WHO, Clinical trials.gov.

Drugs	Mechanism of action
Anti-inflammatory therapies for COVID-19 infection	
Actemra	IL-6 inhibitor
Lenzilumab	anti-GM-CSF
CD24Fc	IL-6 inhibitor
Colchicine	Tubulin disruption
Kevzara	IL-6 inhibitor
Leronlimab	CCR5 antagonist
Aviptadil	IL-6 inhibitor
SNG001	IFN-β-1α
Gilenya	sphingosine 1-phosphate receptor modulator
Mesenchymal stem cells	Tissue regeneration
Gimsilumab	Anti-GM-CSF
Sylvant	IL-6 inhibitor
Anti-viral therapies for COVID-19 infection	
Remdesivir	Adenosine analog
Kaletra	HIV protease inhibitor
Arbidol	Broad-spectrum antiviral
Chloroquine/ Hydroxychloroquine	ACE-2 inhibitor
Avigan	RNA polymerase inhibitor
Pneumonia therapies for COVID-19 infection	
Ganovo-Ritonavir	Hepatitis C/HIV protease inhibitors
Prezcobix	HIV-1 protease inhibitor + CYP3A inhibitor + CYP3A inhibitor
Avastin	VEGF inhibitor
Airuika	PD-1 inhibitor
Plasma therapies for COVID-19 infection	
Plasmapheresis	Antibodies from recovered patients
Therapies for organ failure with COVID-19 infection	
Losartan	AT1R inhibitor
Vaccines under investigation for COVID-19 infection	
mRNA-1273	S-protein mRNA vaccine
Ad5-nCoV	Non-replicating viral vector
ChAdOx1 nCoV-19	Non-replicating viral vector
LV-SMENP-DC	Lentiviral
BCG Vaccine	Live attenuated Virus

patients showed restored levels of NK and $CD8^+$ T cells with a decreased expression of NKG2A. Interestingly, the levels of $CD107a^+$ $CD8^+$, IFN-γ^+CD8^+, IL-2^+CD8^+, and granzyme B^+CD8^+ T cells as well as $CD107a^+$, IFN-γ^+, IL-2^+, TNF-α^+, and granzyme B^+ NK cells were also decreased in COVID-19 patients [52]. Regulatory T cells (Tregs) suppress activated $CD4^+$ or $CD8^+$ T lymphocytes, while IL-10 enhances Tregs and inhibits T cell activation. Decreased levels of Tregs have been observed in COVID-19 patients [53]. IL-10 is an anti-inflammatory cytokine produced in viral, fungal, bacterial, and parasitic infections. It suppresses macrophages and dendritic cells, while inhibiting cytokines and chemokines [54]. IL-10 adjunct therapy has been shown to be effective against viral encephalitis caused by a recombinant coronavirus (J2.2-V-1 [rJ2.2]) in mice [55]. However, elevated IL-10 levels have been observed in COVID-19 patients with severe infection [56], possibly due to a compensatory anti-inflammatory response of IL-10 for high disease severity. Taken together, the evidence strongly supports IL-15 immunotherapy as a useful strategy to control SARS-CoV-2 infection in patients. The rationale is based on our recent findings that IL-15 can induce INF and IL-10 by increasing the number of Treg subsets [17]. Further, mesenchymal stem cells (MSC) possess immunomodulatory effects, and $ACE2^-$ MSC transplantation has showed elevated levels of peripheral lymphocytes and IL-10, as well as decreased levels of C-reactive protein, TNF-α, $CXCR3^+CD4^+$ T cells, $CXCR3^+CD8^+$ T cells, and $CXCR3^+$ NK cells that secrete cytokines. These MSC are ACE2- and TMPRSS2-, and are free from SARS-CoV-2 infection [57]. Therefore, it is helpful to assess cytokines and lymphocyte subsets in the initial screening and treatment of COVID-19.

7. SARS-CoV-2 mediated pulmonary fibrosis

Immune cell infiltration and inflammatory cytokine storms observed in SARS-CoV-2 infected patients can lead to acute pulmonary injury and edema via dysfunctional endothelial barriers and damaged alveolar walls in the lung [58]. The histological features of lung tissues in COVID-19 patients include pulmonary edema, interstitial fibrosis, mucin production, pulmonary hemorrhage, hyaline degeneration, vascular wall thickening, inflammatory cell infiltration, necrotizing bronchial and epithelial cells, and squamous cell metaplasia. Additionally, the pulmonary tissues showed positive staining of CD3, CD4, CD8, CD20, CD79a, CD5, CD38, CK7, and collagen IV [59]. SARS-CoV-2 induced cytokine storms may further lead to clotting, cell death, immune paralysis with inflammation, and organ failure.

8. Current and potential treatments for COVID-19

Humoral and cell-mediated responses are critical in fighting against SARS-CoV-2 infection. Various preclinical studies in mouse models showed protective responses against the S protein of SARS-CoV-2, and antibodies generated against the N protein of SARS-CoV-2 was reported in COVID-19 patients. Azithromycin and hydroxychloroquine combination are more efficient for viral load reductions against SARS-CoV-2 infection [60]. Kaletra anti-viral therapy, along with IFN and antibiotic treatment, has been shown to normalize T cells, NK cells, and NKG2A + Cytotoxic T lymphocytes (CTLs) in a small set of individuals [52]. Increased level of IL-6 is correlated with poor outcomes in COVID-19 patients and a study with IL-6 receptor-targeted antibodies, tocilizumab, has showed recovery of respiratory functions (ChiCTR2000029765) [61]. Cross-neutralizing human monoclonal antibody 47D11 that targets the conserved epitope in the SARS2-S-S1B domain and neutralizes both SARS-CoV and SARS-CoV-2 is identified in cell culture. This antibody alone or in combination with other anti-viral drugs may potentially prevent and/or treat COVID-19 [62]. Furthermore, convalescent plasma transfusion with SARS-CoV-2-IgG antibody and a neutralization titer has been shown to improve symptoms in a small study with 5 patients [63]. Convalescent plasma therapy is well tolerated with increased oxyhemoglobin saturation and lymphocyte counts, decreased C-reactive protein, and neutralized viremia in 10 COVID-19 patients [64]. However, these data are not independently reliable due to the absence of the control groups in these studies. The effectiveness of plasma therapy needs to be validated in reliable double-blind placebo-controlled clinical trials. Natural immunity and anti-oxidative capacity of the host are crucial in minimizing or preventing symptoms associated with viral attacks. Earlier reports have also indicated antiviral properties of micronutrients [65], and a recent study has demonstrated that vitamin D could improve clinical symptoms of COVID-19 [66]. Therefore, maximizing the body's defense with anti-oxidant-rich diets supplemented with micronutrients might be beneficial in some individuals with healthy immune systems [67]. Several ongoing clinical trials across the globe for vaccines, anti-viral drugs, and neutralizing antibodies to restrict COVID-19 infection in humans are listed in Table 1.

9. Conclusions

The COVID-19 pandemic is a worldwide public health concern and is worse than the influenza pandemic of 1918. Almost 382,867 deaths have been reported as of June 04, 2020. Several clinical trials are currently under way in search of therapies for COVID-19. SARS-CoV-2 infection induces cytokine storms via several immune cells. The IL-15 immunotherapy may be a viable strategy for COVID-19, as it promotes innate immune responses via the induction of NK cells, $CD8^+$ T cells, and T regulatory cells to neutralize Th2 cytokine storms, resulting in decreased levels of IL-4, IL-5, and IL-13. These events mitigate SARS-CoV-2 induced inflammation and fibrosis through IFN-γ and IL-10,

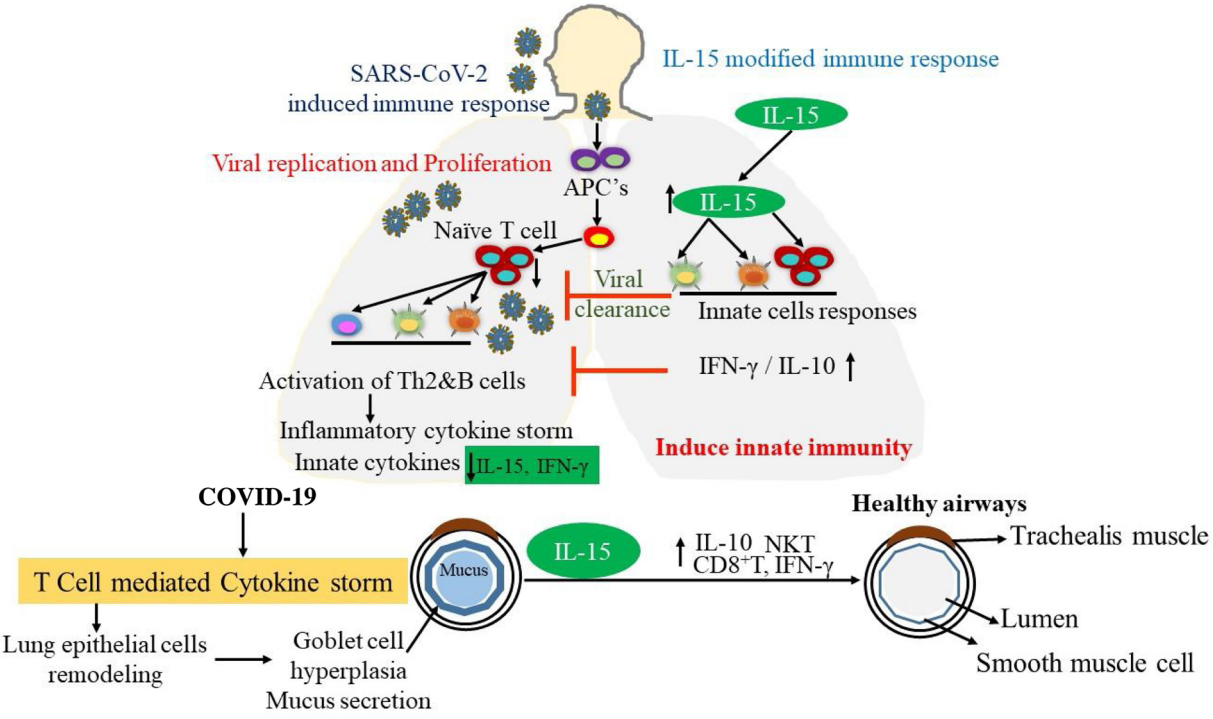

Fig. 4. Significance of IL-15 immunotherapy in inducing innate immunity in COVID-19 patients. In response to SARS-CoV-2 infection, cytokine storms occur via the induction of several immune cells. IL-15 overexpression promotes innate immune responses via the induction of NK, $CD8^+$ T and T regulatory cells that neutralize the induced Th2 cytokine storms, resulting in decreased levels of IL-4, IL-5, and IL-13. These events mitigate SARS-CoV-2 induced inflammation and fibrosis via IFN-γ and IL-10, which inhibit viral replications and reduce viral loads.

which inhibit viral replications and reduce viral loads. The current review highlights the importance of IL-15 immunotherapy in decreasing viral loads and neutralizing cytokine storms induced by SARS-CoV-2 in COVID-19 patients. A summarized mechanistic pathway for IL-15 immunotherapy is presented in Fig. 4.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.06.008.

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