Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Innate and adaptive immune responses against coronavirus

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ABSTRACT

Coronaviruses (CoVs) are a member of the Coronaviridae family with positive-sense single- stranded RNA. In recent years, the CoVs have become a global problem to public health. The immune responses (innate and adaptive immunity) are essential for elimination and clearance of CoVs infections, however, uncontrolled immune responses can result in aggravating acute lung injury and significant immunopathology. Gaining profound understanding about the interaction between CoVs and the innate and adaptive immune systems could be a critical step in the field of treatment. In this review, we present an update on the host innate and adaptive immune responses against SARS-CoV, MERS-CoV and newly appeared SARS-CoV-2.

1. Introduction

In December 2019, Chinese health authorities identified unusual cases of patients with unknown pneumonia in Wuhan City, Hubei Province [1,2]. The clinical symptoms of patients included pyrexia, cough, fatigue, acute respiratory distress, reduced or normal white blood cells, lymphopenia, etc. [1,3]. Subsequent investigations revealed that the source of the disease was the seafood wholesale market at which a wide range of live or freshly animals (such as poultry, bats, and snakes) were slaughtered and sold [1,3]. As it turned out that most cases were directly associated with the Huanan seafood market (e.g. sales people or market managers), the local health authorities issued an epidemiological warning and then the wet market was closed and disinfected on 1 January 2020 [3].

The cause of this unknown disease was temporarily named as the new coronavirus-2019 (nCoV-2019) and unofficially referred to as the Wuhan coronavirus [2]. Genomic analysis of 2019-nCoV exhibited some genomic similarity (79.5 % of the genetic sequence) to the SARS-CoV that caused the 2002–2003 pandemic [2,4]. Then the virus renamed by the International Committee on Taxonomy of Viruses as SARS-CoV-2 and WHO officially called this disease as coronavirus disease 2019 (COVID-19) [2,5].

WHO announced the outbreak of COVID-19 as a global public health emergency on 30 January 2020, sixth after H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016) and Ebola in the Democratic Republic of Congo (2019) [2]. COVID-19 has now been characterized as a pandemic. After that this disease was identified in Wuhan, China on December 2019, it has rapidly spread around the world, except a few small countries and islands. Due to the lack of vaccines and definitive treatment, the number of people dying of lab-confirmed COVID-19 are being increased and most of them are elderly people aged 65 years or more. This is probably due to the fact that they have weak immune system and reduced ability to repair the damaged cells [1,6].

The understanding of the structure of this novel virus and its interaction with immune system is important for the production of drugs and vaccines. Thus, this article aimed to review the current knowledge of the SARS-CoV-2, and present an update on the host innate and adaptive immune responses against SARS-CoV, MERS-CoV and newly appeared SARS-CoV-2.

2. Origin, transmission and structure of SARS-CoV-2

Although there was some initial speculation that SARS-CoV-2 is a laboratory construct and purposefully manipulated by humans, there is

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not a shred of evidence to support such a theory [2]. Some scientists believe that the specific mutation found in the receptor-binding domain of the virus is quite different from what has been predicted based on the genetic systems. It seems currently impossible to prove or disprove theories about the origin of this virus [2,7]. However, what we can say without a doubt as to this disease is that it has originated from a Wuhan seafood wholesale market where wild animals (such as marmots, birds, rabbits, bats and snakes, etc) were sold. Scientists believe that SARS-CoV-2 most likely originated in bats, jumped from this animal to other animals, and then passed it to humans. Although bats are a probable source of this virus, some researchers say that humans are to blame for the spread of COVID-19 all over the world [2,3,8].

This novel virus, SARS-CoV-2, belongs to coronaviruses, which have the crown-like spikes on their surface ("Corona" is Latin for crown or halo) [2]. Based on genomic structure, coronaviruses are classified into four major subgroup, including alpha, beta, gamma, and delta. Alpha- and beta coronaviruses can infect mammals and cause some symptoms in pulmonary and gastrointestinal system in humans and other animals, while gamma, and delta coronaviruses usually infect birds [2,9]. There were only six discovered viruses to infect humans until December of 2019. Four of them including HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1 usually cause mild respiratory symptoms similar to a common cold in immunocompetent people. The other two are SARS-CoV and MERS-CoV that are able to cause severe and fatal pulmonary infections, and have caused pandemics in 2002 and 2012, respectively [2]. Based on genomic sequencing, SARS-CoV shares 79.5 % sequence identity with SARS-CoV [4]. Moreover, it was found that similar to SARS-CoV, this new virus uses angiotensin-converting enzyme 2 receptor for cell entry. These receptors can be found in the in epithelium of lower respiratory tract of humans and regulate the cross-species transmission from snake to human as well as and human-to-human transmission [1,4].

SARS-CoV-2 is a spherical or pleomorphic enveloped particles that contain a positive-sense single-stranded RNA with the size of approximately 29.9 kb [1,10]. Among all known RNA viruses, coronaviruses have the largest genomes (26.4–31.7 kb) [1,11]. Like other coronavirus, this virus has at least six extra open reading frames (ORFs) in its genome. The first ORFs (ORF1a/b) are about two-thirds of the whole genome length and encode 16 nsps (nsp1-16). These ORFs produces two polypeptides, including p1a and pp1ab. One-third of the genome near the 3′-terminus encodes four main structural proteins, including the nucleocapsid, spike, envelope, and membrane proteins; the nucleocapsid protein holds the genome of the virus, and the three other proteins create the viral envelope [11,12]. The structure of coronavirus is shown in Fig. 1. The spike proteins, which cover the outer surface of SARS-CoV-2, play a key role in determining host cells and enable the virus to attach to and fuse with the membrane of them [1,11]. These proteins possess a variable receptor-binding domain (RBD) which bind to ACE-2 receptors found in the respiratory system, gastrointestinal tract, heart, and kidneys [1]. It seems that the RBD of SARS-CoV-2 is a mutated version of its most similar virus (RaTG13) and this mutation has drastically enhanced the RBD affinity to angiotensin-converting enzyme 2 (ACE-2), especially in human lung cells [2,7]. After that this virus attaches to a host cell, the proteases within host cell begins to cut open the spike protein of the virus, exposing a fusion peptide. Then the RNA of virus is released into the cell and the cell is forced to produce more copies of the virus which are widely disseminated in the body to infect more cells [13]. This virus produces some virulence factors that are able to inhibit the immune response [14].

3. Pathogenesis and clinical manifestation

People infected with SARS-CoV-2 have been reported a wide range of clinical symptoms– from mild illness to acute pneumonia. In general, COVID-19 can be studied in three stages: stage 1— asymptomatic state, stage 2— Upper airway responses, stage 3— hypoxia and progression to acute pneumonia [15,16]. At stage 1 (initial two days of infection), patients are asymptomatic but contagious. It seems that the inhaled virus binds to epithelial cells in the nasal cavity within two first days and begins replicating. This local proliferation of the virus is able to induce a limited innate immune response. Although the viral load is usually low during early days of infection, SARS-CoV-2 can be detected by nasal and throat swabs and this might be valuable for predicting the subsequent clinical course [15]. In the next few day (stage 2), the virus migrates down into the lower respiratory tract, and induces innate immune responses more and more. At stage 2, the clinical manifestations of COVID-19 disease can be clearly observed [15]. Some innate response cytokine (e.g. CXCL10) might be useful prognostic and predictive markers for subsequent infectivity and clinical course [17]. These predictive markers may also help physicians to decide whether patients need more aggressive monitoring or not [15]. Usually, more than 80 % of infected people have mild symptoms and should be monitored at home but nearly 20 % of them progress to stage 3 disease and even develop acute pneumonia. According to initial estimates, the mortality rate from COVID-19 in the general population is about 2%, but this varies noticeably in the elderly and people with underlying disease [15,16]. It should be noted that some of infected people are asymptomatic

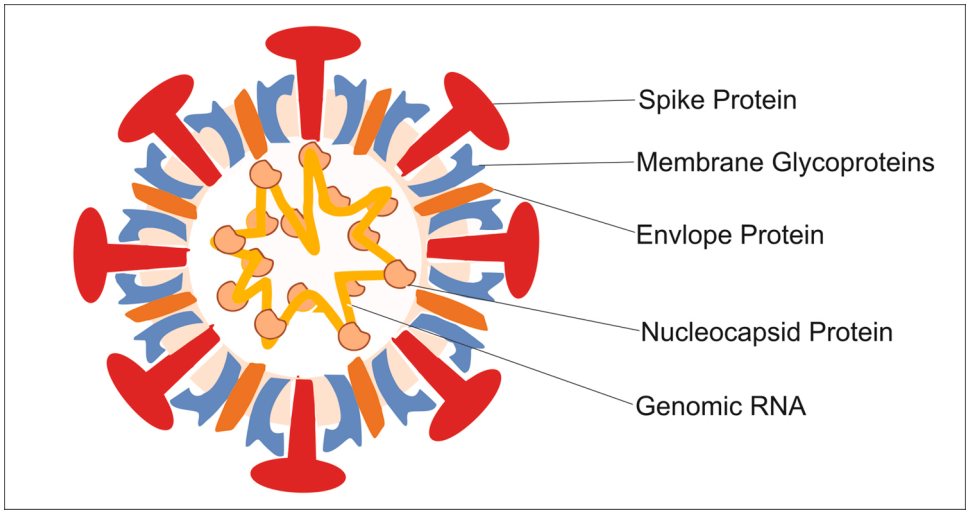

Fig. 1. Schematic structure of SARS-CoV-2. SARS-CoV-2 is a spherical or pleomorphic enveloped particles that contain a positive-sense single-stranded RNA with the size of approximately 29.9 kb. The nucleocapsid protein holds the genome of the virus, and the three other proteins, including spike, membrane and envelope proteins, create the viral envelope.

and not detected by health systems because these individuals do not go to hospitals and clinics to be examined by doctors. Thus, the fatality and morbidity rates need to be revised [15]. At stage 3, SARS-CoV-2 reaches the functional or gas exchange unit of the lung, which consists of alveolar ducts, alveolar sacs and alveoli [15,18]. It seems that this virus preferentially infects alveolar type 2 cells in comparison with other cells [19]. The propagation of the virus within type II cells and consequently the release of a large number of viral particles cause these cells to undergo apoptosis and die [15]. Most researchers express their views concerning the pathobiology of COVID-19 on the assumption that SARS-CoV-2 enters the cell similar to SARS-CoV. Overall, there are critical gaps in current knowledge of the pathogenesis of COVID-19 that need to be discovered.

4. Innate immune responses to coronavirus infection

SARS-CoV-2 (COVID-19) is a concern for global public health due to the lack of efficacious therapeutic strategies and antiviral vaccine. Accumulated evidence showed that patients with COVID-19 have an immune response dysregulation which leads to the development of viral hyperinflammation [20]. Therefore, evaluating hyperinflammation in patients with COVID-19 using laboratory parameters helps to improve mortality [20]. In an study with 452 COVID-19 patients in Wuhan, increased neutrophil counts with higher neutrophil-to-lymphocyte ratio (NLR), increased inflammatory cytokines, i.e., interleukin (IL)-6 and tumor necrosis factor (TNF)-α, as well as reduced monocytes, eosinophils and basophils were reported [20,21]. In another report 41 COVID-19 patients from Wuhan, it was demonstrated that increased levels of neutrophil in ICU vs non-ICU was statistically significant and may associate with disease severity and mortality [22]. However, more studies with high number of patients are needed for precise conclusion.

While SARS-CoV-1 and SARS-CoV-2 mainly use human receptor-angiotensin converting enzyme II (ACE2) as a cellular entry receptor, MERS-CoV enters the cells using dipeptidyl peptidase 4 (DPP4) as a specific receptor [23,24]. ACE2 is presented in lung and gastrointestinal tract that contributed to tissue injury [25]. Damage to the lungs seems to occur by SARS-CoV destruction of macrophages, alveolar and bronchial epithelial cells [25]. However, other receptors may also be involved in the virus entering the cell.

The innate immune cells express pathogen-recognition receptors (PRRs) to sense pathogen-associated molecular pattern (PAMP) that include C-type lectin receptors, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs) [26,27]. RNA viruses, such as coronavirus, are recognized by cytosolic and endosomal RNA sensors, including RIG-I and TLRs (TLR2, TLR3 and TLR7), respectively [28–30]. It is demonstrated that the activation of TLR3 with the polyinosinic-polycytidylic acid (poly I:C) can inhibits infection related-coronavirus [31]. RNA virus recognition by TLRs and RIG-1 results in the activation of the transcription factors, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and interferon regulatory factor 3 (IRF3), leading to translocation into the nucleus, and inducing the expression of pro-inflammatory cytokines, chemokines and type I IFN [32]. Type 1 IFN production in monocytes/macrophages and dendritic cells is shown in details in Fig. 2.

Type 1 INF is considered to be the first antiviral defensive line. Type I IFNs via IFNα/β receptor (IFNAR) activates the janus kinase (JAK), signal transducer and activator of transcription (STAT) signaling pathway [33,34]. Upon IFNAR signaling, JAK1 and TYK2 phosphorylate

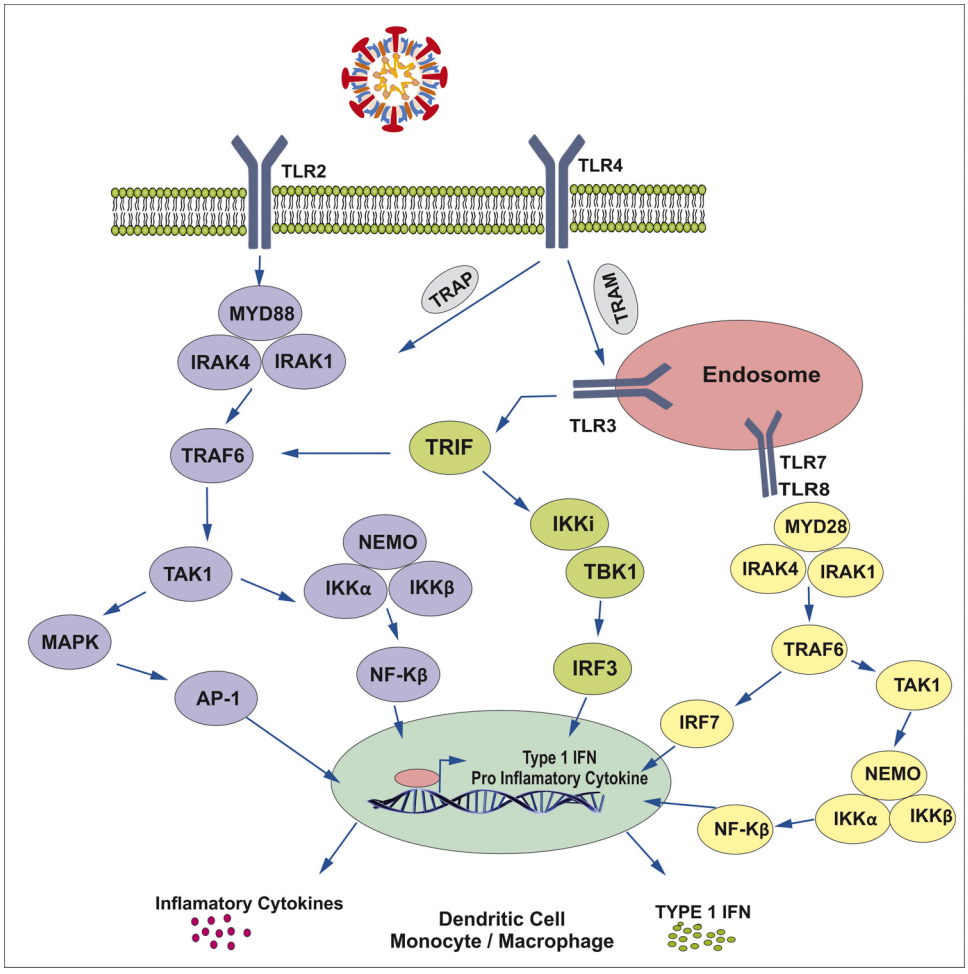

Fig. 2. Type 1 IFN production in monocytes/macrophages and dendritic cells. TLR4 and TLR2 localize on the cell surface, and TLR3, TLR7 and TLR8 localize in the endosome. TLRs signaling initiate upon ligand binding. TLR2 and TLR7/8 engagement induce formation of MyD88, IRAK1 and IRAK4. IRAKs then activate TRAF6 and TAK1. TAK1 leads to the activation of MAPKs and IKK complex consisting of NEMO, IKKα and IKKβ. The MAPK and IKK complex activation lead to AP-1 and NF-kB transcription factor activation, respectively. TLR7 and TLR8 can also induce IRF3 transcription factor activation. TLR3 requires TRIF for IRF3 phosphorylation, which this adaptor protein interacts with IKKi, TBK1. TRAM is required for signal transduction from TLR4 to TRIF, and TRAP is required for signal transduction from TLR4 to MyD88. Finally, transcription factors move into the nucleus and stimulate gene expression. IRF3 and IRF7 induce type 1 IFNs genes expression, and AP-1 and NF-kB induce pro-inflammatory cytokines genes expression.

STAT1 and STAT2 molecules, which form a complex with interferon regulatory factor (IRF) 9 [33,34]. These complexes were entered into the nucleus to stimulate the transcription of IFN-stimulated genes (ISGs) and subsequently the expression of antiviral proteins [33,34]. A number of ISG products, including IFN-induced transmembrane (IFITMs) proteins 1, 2, and 3, restrict infection mediated by the SARS-CoV [35,36].

However, highly pathogenic coronaviruses, SARS-CoV and MERS-CoV, employ various strategies to suppress the antiviral type 1 IFNs responses. Upon SARS-CoV and MERS-CoV infection, dendritic cells (DCs) and macrophages show low-level expression of IFN-α/β responses [37,38]. Using SARS-CoV-infected mice, it is demonstrated that the dysregulation of type I IFN induction is responsible for the lung immunopathology [39]. During infection, while plasmacytoid dendritic cells (pDCs) are the major source of type I IFNs, various nonstructural proteins of SARS-CoV modulate IFN responses in pDCs and other immune cells [37–39]. For SARS-CoV, non-structural proteins, including ORF6 and nsp1, interfere with the IFN signaling through inhibiting the phosphorylation of STAT1 and subsequent STAT1 transport into the nucleus [40,41]. In MERS-CoV, the structural (such as M) and non-structural (such as ORF 4a, ORF 4b, and ORF 5) proteins are potent IFN antagonists [42]. It is revealed that the ORF4a protein counteract the antiviral effects of type 1 IFNs via inhibition of the transcription factors, IRF3/7 and NF-kB, activity [35,42].

High serum levels of chemokine and cytokine in patients with severe cases of SARS-CoV or MERS-CoV infection suggesting that possible enhanced and dysregulated chemokine and cytokine responses could promote lung pathology. SARS-CoV infected-macrophages produce the chemokines such as chemokine C–C ligand 2 (CCL2)/monocyte chemotactic protein (MCP) 1 and C-X-C chemokine (CXCL10)/IFN- γ -inducible protein 10 (IP-10) [43]. The up-regulation of CCL7/MCP-3, CCL8/MCP-2 and CCL3/macrophage inflammatory protein (MIP)1α was also observed in SARS-CoV. These produced chemokines have chemotactic activity for macrophages [44].

MERS-CoV induces the expression of cytokines (TNF-α, IL-6, IL-12 and IFN-γ), and chemokines (MCP-1/CCL-2, regulated on activated normal T-cell expressed (RANTES)/CCL-5, MIP-1α/CCL-3, IP-10/CXCL-10 and IL-8) in human macrophages [45]. The production of these inflammatory cytokines and chemokines could be an important factor in the MERS-related disease pathogenesis [45]. A increased cytokine profile, including IL-2, IL-7, IFN- γ, IP-10, TNF-α, MIP-1 α and MCP-1, is also showed that is related with COVID-19 disease severity [46].

Furthermore, eosinophils and natural killer (NK) cells have antiviral activity. Eosinophils limit respiratory syncytial virus (RSV)induced lung disease through production of nitric oxide (NO) by nitric oxide synthase 2 (NOS-2) [47]. NK cells express various receptors for MHC class I, which can either inhibit or activate cytokine production or cell-mediated cytotoxicity [48]. NKG2D (natural-killer group 2, member D) is one of activating receptor that enhances cytokine production, chemokine secretion and cytolytic activity of NK cells [49]. CXCL10 induces innate immune responses, including NK cells, following viral infection [50]. Walsh et al. demonstrated that in mouse hepatitis virus (MHV)-CXCL10-infected mice, increased NK cell IFN-γ production within the brain occurs independently of NKG2D [49]. In the liver of MHV-infected mice, NKG2D signaling induces antiviral activity and control of the virus replication [49].

The exact role of innate immunity against COVID-19 is not fully understood. Given that individuals with underlying diseases are more susceptible than healthy people or young children to severe disease because of the low efficacy of innate immune response [19]. It could be postulated that innate immune responses play a critical role in the disease outcome. Furthermore, severe COVID-19 cases had elevated the levels of various innate cytokines, including granulocyte colony stimulating factor, IP-10, TNF-α, MIP-1α and MCP-1 [46]. These laboratory findings suggested that increasing in pro-inflammatory cytokines may be correlated with disease progression, severity and death, so COVID-19 is considered as a cytokine storm-mediated disease [51]. To initiate this complex process, a stimulus such as microbial pathogen damages the barrier sites such as lungs or gut [52]. The innate immune cells response to tissue damage or microbial invasion by the production of several cytokines, including IL-1, IL-6 and TNF [52,53]. These cytokines will induce T and NK cells production of pro-inflammatory cytokines, including IL-2, GM-CSF and IFN-γ [52,53]. This high levels of pro-inflammatory cytokines results in mobilization of various immune cells such as neutrophils, macrophages and T cells from the blood circulation into the infected tissue that lead to diffuse alveolar damage, capillary damage, vascular barrier damage, multiorgan damage and ultimately death [54]. SARS and MERS are also cytokine storm-mediated disease, and the levels of pro-inflammatory cytokines in patients' serum were increased similar to COVID-19 [55–57].

5. Adaptive immune responses to coronavirus

T cells, CD4+ and CD8 + T cells play a critical antiviral role through promoting the secretion of pathogen-specific antibodies by inducing T-dependent B cells and killing the virus infected cells, respectively [58]. The importance of CD4 + T cells in controlling SARS-CoV replication and disease severity has been shown by using T-cell-deficient BALB/c mice [59]. It emphasizes the essential role of CD4 + T cells in primary SARS-CoV infection [59]. Although, virus-specific CD4 + T cells are important for complete virus clearance, virus-specific memory CD8 + T cells have significant role in host protection from lethal SARS-CoV infection by multiple cytokines (IFN-γ, TNF-α and IL-2) and cytolytic molecules (granzyme B) production [60]. In addition, memory CD8 T cell responses against SARS-CoV structural M and N proteins persist in recovered individuals up to 11 years with ability of proliferation and IFN-γ production even in the absence of the antigen [61], while, in COVID-19, total T cell counts, CD4 + and CD8 + T cells are significantly reduced [62]. COVID -19 consider as cytokine storm disease, as previously mentioned [46]. Diao et al. suggested that the cytokines including TNF-α, IL-6 and IL-10 may promote necrosis or apoptosis of T cells, and leads to their reduction [62]. A Bcl-2 homology domain 3 (BH3)-like region located in the C-terminal cytosolic domain of SARS-CoV E protein interacts with Bcl-xL and induce T-cell apoptosis [63]. MERS-CoV can also induces T cell apoptosis by promoting extrinsic and intrinsic apoptosis pathways [64]. Therefore, reduction of T cells induce viral survival and prolong the coronavirus-related infection. Additionally, the induction of T helper (Th) 17 cytokines, such as IL-17, has been reported in MERS-CoV [64]. These Th17 cytokine recruit monocytes and neutrophils to the site of inflammation or infection and activate other downstream chemokine and cytokine cascades, such as TNF-α, IL-1, IL-6, IL8, and MCP-1 [64]. In COVID-19, the number of CCR6+ Th17 cells increases and promotes the cytokine storm, which results in pulmonary edema and tissue damage [65]. Wu et al. suggested that Fedratinib (a JAK2 inhibitor) can prevents the production of Th17 related cytokines, including IL-17 and IL-22, and reduces mortality of patients with COVID-19. A large amount of pathogenic Th1 cells are also seen in the lungs of COVID-19 patients, which causes lung dysfunction and quick mortality [23]. CD4 + T cells rapidly become pathogenic Th 1 lymphocytes and produce granulocyte-colony stimulating factor (G-CSF) cytokine [23]. It is also showed that CD8 + T cells from ICU patients infected COVID-19 have higher GM-CSF expression compared to those from healthy controls and non-ICU patients [23]. GM-CSF involves in the pathogenesis of COVID-19 infection and initiates tissue damage [23]. In addition, CD4 + T cells and CD8 + T cells from COVID-19 patients are functionally exhausted and express high levels of exhaustion markers including Tim-3 and PD-1 on cell surface [62]. Taken together, T cells are reduced and exhausted in coronavirus related diseases and can be associated with more severe symptoms or mortality.

Humoral immunity is required for controlling CoVs infections, but little is known as yet about it. In SARS-CoV, antibody profile shows a typical pattern of IgM and IgG secretion [66]. The SARS-specific IgG antibodies can exist for a long time than IgM, indicating that IgG

antibodies play a protective role [66]. The innate and adaptive immune responses against Coronavirus infection is shown in Fig. 3.

The convalescent plasma (CP) therapy, including neutralizing antibodies, is not new, and previous evidences showed that the use of CP therapy could decrease mortality rates in patients with SARS, MERS, avian influenza A (H5N1) and Ebola [67]. However, in COVID-19, the efficacy and safety of CP therapy have not fully been known. Ye et al. reported outcomes of 6 COVID-19 patients who received ABO-compatible CP from recovery patient in Wuhan [68]. CP transfusion in them led to a radiologic improvement and clearance of SARS-CoV-2 in the upper respiratory tract [68]. In addition, the anti-SARS-CoV-2 antibody titers increased after convalescent plasma therapy [68]. Furthermore, no serious adverse effects were reported during the treatment [68].

In a pilot study one dose of 200 mL CP transfusion increased lymphocyte counts and decreased C-reactive protein [69]. CP has also a therapeutic potential in critically ill patients with SARS-CoV-2 infection, which reduced viral load, improved chest imaging and decreased body temperature [70,71].

Although there is several studies which have indicated that CP therapy could improve laboratory parameters, radiologic and clinical features, but still CP transfusion risk, such as aggravating hyper-immune attacks is remaining [72,73]. Antibody-dependent enhancement (ADE) is an atypical immunological phenomenon where preexisting and non-neutralizing coronavirus-specific antibodies increase the pathology of SARS-COV-2 disease [74]. ADE is occurred by the engagement of Fcγ receptors (FcγRs) expressed on immune cells like macrophages, monocytes and B cells and promote the virus uptake into cells [75]. This uptake enhance virus replication by these immune cells and ultimately leads to dysregulation of immune responses to COVID-19 and worsening clinical symptoms [76]. Therefore, the geographical discrepancy of disease severity can be explained by ADE [77]. In addition, several adverse reactions, including transfusion-related acute lung, fever, chills, anaphylactic reactions and hemolysis, have been reported [72]. However, overall success in CP therapy leads to the development and use of monoclonal antibodies.

Recently, Jawhara et al. showed that passive immunotherapy with immune IgG antibodies combined with antiviral drugs will be effective against COVID-19 infection by boosting the immune responses [78]. Results from various studies have reported more than 20 kinds of monoclonal antibodies (mAbs) [57]. The spike glycoprotein is the best target for vaccine designs against coronaviruses [79]. The mAb m336 competes with the receptor DPP4 for binding to the spike glycoproteins and inhibits infection with MERS-CoV [80]. Human mAb m336 reduces the viral titer in the respiratory tract [81]. Mice inoculated with Purified coronavirus spike protein nanoparticles produce high titer neutralizing antibodies against the homologous virus, but these antibodies have no cross-protection against the heterologous virus [79]. After MERS-CoV infection, marmosets treated with high hyperimmune plasma or the mAb m336 show a reduction in disease severity [81]. It is also demonstrated that vaccination ferrets with recombinant modified vaccinia virus Ankara (rMVA) expressing the SARS-CoV spike glycoprotein can induce vigorous and rapid neutralizing antibody responses, however the strong inflammatory responses have been observed in liver tissue. Therefore, the expression of SARS-CoV spike protein is associated with enhanced hepatitis [82]. The combination of neutralizing mAbs CR3014 and CR3022 targeting the receptor-binding domain (RBD) of SARS-CoV potentially control viral infection with a high level of safety and efficacy [83].

So far, no specific antiviral vaccines or drugs regime have been developed for SARA-CoV-2 [84]. However, passive immunotherapy could be an useful therapeutic option against the COVID-19 pandemic until effective and definitive treatment is found [85,86]. Tian et al. reported that CR3022 mAb targeting the RBD of COVID-19 has the potential to control the viral related disease [87]. Therefore, combinations of CR3022 with other neutralizing antibodies considered as a candidate in the treatment of the COVID-19 [87]. Wang et al. also showed that human 47D11 mAb binds to spike protein of SARS-CoV-2 and potently inhibits of virus infection [88]. Wu et al. reported four human-origin mAbs (H2, H4, B5 and B38,) from a convalescent patient, which all of mAbs showed neutralization abilities [89]. H4 and B38 complete block the binding between ACE2 and virus S-protein RBD [89]. In contrast, B5 has partial competition, while H2 did not compete with the RBD-ACE2 [89]. Given IL-6 plays a critical role in cytokine storm, IL-6 receptor

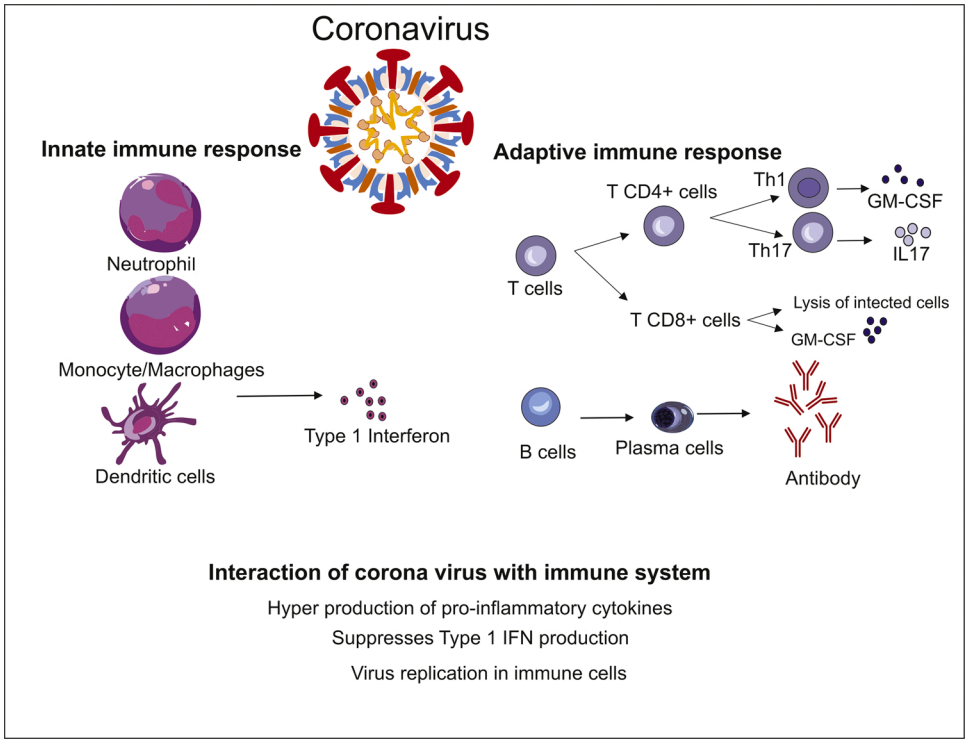

Fig. 3. The innate and adaptive immune responses against coronavirus (CoV) infection. The induction of neutrophils, monocytes/macrophages and dendritic cells results in production of various pro-inflammatory cytokines which so-called "cytokine storm". This process leads to lung immunopathology. Specific CD + Tcells, Th1 and Th17, may be activated and exacerbate lung injury. Cytotoxic T-lymphocyte (CTL) contributes to virus clearance by lysis of infected cells. B cells produce virus specific antibodies and neutralize viruses.

antagonist tocilizumab may be an effective drug for the treatment of severe COVID-19 [90,91].

6. Conclusion

The SARS-CoV was seen in 2002 and spread to 32 countries, then MERS-CoV caused problems in the world, and now, the SARS-CoV-2. Since CoVs induce serious infectious and spread rapidly, it has become a global threat to human health due to the lack of efficacious antiviral vaccine and drugs. In recent years, the role of innate and adaptive immune responses to CoVs have been understood. Both immune responses induce virus clearance, inhibit virus replication and promote tissue repair. However, the immune responses also play an important role in SARS-related pathogenicity. As previously mentioned, the SARS-CoV-2 is referred to as cytokine-mediated disease, therefore, in CoVs, it is critical to control immune and inflammatory responses. Until the deep understanding of the role of the immune cells, therapeutic strategies for the CoVs will be challenging. Achieving this goal is not impossible, and even significant achievements have been made in this area. For instance, using of interferon-inducing agents could regulate the host responses and reduce mortality of SARS-CoV-2, in which IFN-γ combination with type 1 IFN maximize the effects [92]. More researches are needed in order to achieve the better understanding of the immune responses to validate the best therapeutic interventions.

Declaration of Competing Interest

There is no conflict of interest.

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