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Review Article

An Overview on Pathogeneses, Immune Responses, and Challenges against SARS-CoV and SARS-CoV-2: a narrative review

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Abstract

Coronaviruses are a large family of viruses known to cause illnesses ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). A novel coronavirus (COVID-19) was identified in 2019 in Wuhan, China. This is a new coronavirus that has not been previously identified in humans. The statistics of this disease to date are 516 million cases and 6.25 million deaths.

To recognize the reasons for severe illness experiences in some patients, it is offered to have a review on pathogeneses (different mechanisms of adherence to host cells and detecting affiliated

receptors), other responses of the innate immune system, leading to cytokine storm, inflammations, and a confused and unable system to identify and eliminate infectious organisms and all the pathogens, as the main reason in acute respiratory distress syndrome. Identifying immunopathogenesis characteristics of the virus can help us know more about new therapeutic medicines and patient outcomes.

Keywords: SARS-CoV, SARS-CoV-2, Pathogenesis, Immune Challenges ,Cytokine Storm

Introduction

Coronavirus 2019 (COVID-19), also known as acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) as one of the most substantial global health threats since December 2019, was observed with pneumonia-like illnesses with severe and obscure respiratory symptoms in Wuhan, China for the first time. Approximately one month later, it was determined that the cause of the disease was coronavirus which was genetically similar to the SARS, leading to name the pathogen ephemerally as 2019 novel coronavirus (2019-nCoV) (1), showing clinical signs such as fever, respiratory symptoms like cough, sore throat, asthma, and sometimes gastrointestinal problems (2). Subsequently, China came up with a rapid increase in the number of cases (77,780 cases and 2,666 deaths during February 2020), resulting in that COVID-19 being reported as a Public Health

Emergency of International Concern (PHEIC) and a pandemic by WHO (3, 4). Numerous researches were gradually launched to study the diverse aspects of this disease. After more than two years of the first RT-PCR positive case, the investigations are still going on. This article intends to review studies about pathogeneses and immune challenges of COVID-19.

Pathogenesis of COVID-19 infection

It is thought that any theories covering COVID-19 pathogenesis should delineate highly significant serum levels of both ferritin and D-dimer levels disparate with the difficulty of infection, as well as a tendency for monocytosis, rather than lymphocytosis, containing a few numbers of natural killer (NK) and cytotoxic T cells, and lastly tendency for disseminated intravascular coagulation (DIC). These characteristics are generally the leading causes of cytokine storms (5).

Having a positive-sense single-stranded RNA genome , the virus typically pursues a five-step system to adhere to host cells viz attachment, penetration, biosynthesis, maturation, and release (6). Moreover, it has been made out that these viruses have four structural proteins composing E, M, N proteins and S-Spike glycoprotein, which the last one has a great magnitude in terms of the pathogenesis of coronavirus (and SARS-CoV-2) due to expediting and mediating of receptor detection, attaching to the membrane receptor and fusion with the cellular membrane (7, 8). In an ordinary and native status, the S protein is indeed an inactive precursor. To activate it, the proteases of attacked cell and cleave the S protein into S1 and S2 subunits (responsibility for binding the virus to the receptor and virus fusion, respectively), leading to causing unnormal circumstances (like viral infection) (9-11)According to the resultant studies, the four possible entry molecules (host cell receptors and host proteases) to facilitate the invasion of SARS-CoV-2 are the following points: (i) ACE2, (ii) TMPRSS2, TMPRSS4 and Furin (the host proteases), (iii) GPP78, and (iv) CD147 which have been explained in the **Table. 1** (12).

While spreading the virus, the immune system detects viral antigens and fights against them through T cytotoxic cells and antibody production. The level of immune system function, disease severity, and various factors involved cause immunity against the virus. Also, large amounts of pro-inflammatory cytokines and chemokines are substantial. In some people, this function is so

severe that it causes a cytokine storm, followed by thrombosis and organ failure, and ultimately leads to death (5, 13).

Another different pathogenic mechanism has also been suggested. The virus links to the beta chain of porphyrins inside red blood cells, disrupt cell metabolism and release iron globules (14).

Herd immunity; right or wrong?!

As an indispensable expression in epidemiology to burn out or cease an outbreak, Herd immunity can be reached in two ways: through natural infection and/ or vaccination (15). Many immunity studies have been carried out after COVID-19, the consequences of which demonstrate that herd immunity as a method to deliberately expose people to infection to induce natural safety against COVID-19 is vigorously rejected for distinct reasonings by many ethicists and WHO and is known as an unethical strategy, because large numbers of people must be exposed to the disease to assess its safety; therefore it is vague when protection will be achieved, and it depends on the number of people who become immune after COVID-19, resulting to how many people will die to achieve herd immunity? It has not yet known precisely whether the disease gives immunity to future infections and how long immunity will last (16).

Immunity to coronaviruses is usually short-term. For instance, searches of survivors of the SARS-CoV epidemic indicated that patients who were IgG positive were kept in >90% of the patients for two years (17). But, another study showed that six years later after infection, SARS-CoV antibodies were not found (18).

On the other hand, in comparison, inducing herd immunity with vaccination (emphatically far-reaching availability of vaccine; sometimes called as "the Ring of Vaccination") is a much safer and more base-on-evidence strategy to provide herd immunity resulting in frustrating the new waves of COVID-19 (19).

Immunity to COVID-19 is a mystery. According to recent data, the majority of recovered patients develop antibodies to SARS-CoV-2. However, scientists are unsure if anyone creates enough antibodies to ensure future safety, what a healthy degree of immunity is, or how long immunity lasts. Based on immune responses to closely associated viruses such as those that cause SARS and

the Middle East respiratory syndrome (MERS), current estimates indicate that recovered individuals could be shielded from re-infection for one to two years. However, if SARS-CoV-2 tolerance is more like that of the common cold, the security time could be cut in half (20).

Immune responses against COVID-19

- **Innate immunity**

The immune system is a complex of interconnected cells with consistent functions to protect the body against internal and external threats and intruder's agents and is generally divided into two important categories: innate (or natural/ native) and adaptive (or acquired) immunities. Understanding these immune responses and immunological pathways will help to the progression of useful and therapeutic approaches or the design of effective vaccines against COVID-19.

The innate immune response is known as the first important line of defense for the host against many different infectious agents that can quickly identify pathogens at the moment of arrival and destroy them through various defense mechanisms (21). The innate immunity also invokes the adaptive immune system to continue immune responses via sending molecular signals (cytokines, chemokines production) or signals associated with the residual products of infectious pathogens (antigens) under a process called "antigen presentation". Undoubtedly, without these signals, the adaptive immune system cannot be activated. In the chronic and severe conditions of the disease, the innate system is confused and unable to identify and eliminate infectious organisms and all of the pathogens.

Although the exact function of the immune response to SARS-CoV-2 is unknown, elevated levels of proinflammatory cytokines, called "cytokine storms," due to overactive myeloid cells associated with thrombosis and vascular permeation increase morbidity and mortality (22, 23). Hyperactivity of myeloid cells and cytokines/chemokines lead to hyper-inflammatory states and increased complement activation. Elevated activity of the complement system plays a destructive role in SARS-CoV-2 infection and can significantly induce inflammation-mediated tissue damage during COVID-19. However, the exact mechanisms of hyper-inflammatory are complex and are not fully clear (24, 25).

Initiation of innate immunity mediated by pathogen-associated molecular patterns (PAMPs), small conserved molecular motifs specific to pathogens and act as ligands, which are recognized by some molecules named pattern recognition receptors (PRRs) encompassing five primary families: Toll-like receptors (TLRs), a retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors and absent in melanoma 2 (AIM2)-like receptors (26), resulting in introduction and production of cytokines and chemokines and eventually the death of the cell(27). Linkage of ligands to specific receptors induces the signaling pathways that stimulate the expression of transcription factors such as NF-kB, IRF3, and AP-1, which synergistically augment the type I interferon (IFN-I), (IFN -α,β), secretion. which all of these processes have been outlined in **Figure. 1** (**a-c**) (27): a delineation of TLRs (28-32), of RLRs and IFN signaling (33-36), and of NLRs and inflammasome sensors (37-42)**.**

These cytokines induce the expression of interferon-stimulated genes (ISGs) in a paracrine manner. ISGs are considered an essential component of innate antiviral defense that have an important role in the prevention of viral entry and inhibiting viral replication within the host cells. A recent study represented that ACE2 acts as an ISG in severe infections, SARS-CoV-2 may recruit IFN-associated ACE2 up-expression to raise the infectious status. (43-45). Coronaviruses (CoVs) interfere with the normal function of the immune system and manipulate the production and secretion of interferons families. Clinical results showed that COVID-19 patients with impaired IFN-α production experienced a more severe form of infection (46, 47) .Different types of IFNs, especially type I IFNs, inhibit SARS-CoV-2 proliferation more effectively in vitro and have potential antiviral activity than type IFNs and generate beneficial and satisfactory responses against SARS-CoV-2 infection without the creation of inflammatory states and tissue damage(48, 49)

CoVs by the several structural and non-structural proteins acting as interferons antagonists. These CoVs also by disturbance of pattern recognition receptor (PRR) signaling and TLR-induced signaling pathways create an inflammatory cascade that leads to cytokine storm and augments lung injury while inhibiting induction of interferons -antiviral responses. Elevated levels of pro-inflammatory cytokines and other inflammatory factors such as IL-2, IL-7, G-CSF, MCP-1, MIP-1a, IP-10, and TNF-a have been closely correlated with pneumonia and lymphopenia, abnormally low counts of lymphocytes, and more severe infection. These pro-inflammatory

mediators summon the innate immune cells, including neutrophils and other myeloid cells, into the lung, to excite potent local inflammatory responses. Similar to SARS and MERS infection, cytokine storm and lymphopenia exhibit a pivotal role in the pathogenesis of COVID-19 **(Figure. 2)** (50)**.** In addition to manipulating cytokines, CoVs affect the function of innate immune executors such as neutrophils, Natural killer (NK) cells, Macrophages, and other immunological interactions including the capturing and presentation of antigens by professional APCs (51). This section attempted to explain the function of known innate immune cells affected by the COVID-19 infection.

Neutrophils infiltration is an early stage of innate immunity against COVID-19 infection. Although the causes of this are unclear, according to the current reports, neutrophil infiltration and related markers are significantly boosted in autopsied SARS-CoV-2 patients. It should be noted that the pathological effects of neutrophils are more closely related to the enhancement of neutrophil extracellular traps (NETs), termed NETosis, which are increased in inflammatory diseases such as sepsis, thrombosis, asthma, and respiratory failure and are involved in the tissue damage and mortality in COVID-19 patients. Increased expression of some cytokines, including IL-6, as an inducer of NETosis, contributes to severe COVID-19 infection. In addition, analysis of bronchoalveolar lavage (BAL), sputum, and peripheral blood mononuclear cell samples from COVID-19 patients showed that levels of specific chemokines such as CXCL2,8 were increased in these patients. Elevated levels of mentioned chemokines invoke more neutrophils into the lungs, intensifying inflammatory responses through various mechanisms such as complement activation.

(52-54) .

Natural killer (NK) cells, the important innate lymphoid cells (ILCs), play a fundamental role in the anti-tumor and anti-viral immune responses against cancers and infectious diseases, and their impaired functions are associated with the increased susceptibility to the kinds of infections (55, 56). Recent evidence showed that the numbers of peripheral blood NK cells are decreased in severe COVID- 19 patients (56-58). Additionally, the expression of some receptors on the plasma membrane of NK cells such as Fc gamma RIII (CD16) and killer-immunoglobulin-like receptors (KIRs) is reduced during the SARS-CoV-2 infection. Since the cytotoxic activity of NK cells is under the control of inhibitory and activating receptors and their ligands on target cells, the dysfunctionality of these receptors interferes with the normal activity of NK cells against

viral/tumor cells. Down-regulation of activating NK receptor expression is an important trick by which viruses escape from NK-mediated killing, as well as, disrupting the maturation and transport of circulating NK cells into the peripheral tissues of COVID-19 patients (59-61). Migration of the NK cells from blood to tissues or lymphoid organs is regulated by chemokines, cytokines, and their corresponding receptors, that exhaust various NK subsets to the inflammatory milieu, chronic viral infection, and tumor microenvironment (60, 62). For example; Increased plasma concentration of the number of IL-6, IL-1, decrease NK cell expression in SARS-CoV-2 infection. Indeed, expressed IL-12 by macrophages / dendritic cells (DCs) contributes to NK cell proliferation, cytotoxicity, survival, and IFN-g production which can limit SARS-CoV-2 infection (63-65). As well as, The expression of inhibitory receptor CD94:NKG2A on NK cells, HLA class I specific receptor, during NK cell differentiation, lead to normally functional exhaustion of NK cells against cancer, severe viral infection, and SARS-CoV- 2 infections (56, 66, 67). Although the exact role of stimulated NK cells in SARS-CoV-2 patients is not fully understood, it seems that the number of these cells and their activity in COVID-19 have been decreased. Anti-S protein antibodies are able to induce NK cell-mediated antibody-dependent cytotoxicity in SARS-CoV-2 infection. This suggests that functional NK cells most likely contribute to the protective immunity against SARS-CoV-2 (68, 69).

Macrophages are considered to be the primary executive agents of innate immunity in response to CoVs infection, which stimulate hyper-inflammatory responses or macrophage activation syndrome (MAS) and are among the first immune cells to encounter incoming viruses in the lungs and upper respiratory tract (70, 71). Emerging studies during the SARS-CoV-2 pandemic suggest that macrophages, as the master enhancers of hypercytokinemia, potentially play a pivotal role in pathogenesis and increasing the number of severe infections, leading to high mortality in COVID-19 patients (72). Macrophages through different mechanisms including IFN_s expression and initiation of inflammatory responses, recruit other immune cells to develop supplementary immune responses (73, 74). During SARS-CoV-2 infection, macrophages are different in children compared to adults or aging and peaking in the lung at the three “developmental surges”.Each of the surges possesses a distinct origin in different locations. Macrophages also express different surface markers and have different membrane receptors dependent upon their subgroups and the status of their local environment. Some macrophages have been shown to have ACE2 receptors, while some do not, but the main causes are unclear (75).

Lung macrophages are classified into two subgroups: alveolar macrophages (AMs) and interstitial macrophages (65). Alveolar macrophages are the most common and best-studied subsets that are accumulated in the alveolar lumen, are in direct contact with air and the environment; interstitial macrophages which comprise 30-40% of lung macrophages, have roles in tissue regeneration and maintenance, as well as are involved in the antigens presentation by DCs. They are very different from AM in terms of gene expression and tissue localization. These two subgroups are separated only by a thin alveolar wall. interstitial macrophages are divided into two classes: Nerve-and airway-associated macrophages (NAMs) which are most probably important for limiting viral-induced inflammation in response to CoV's. NAMs are located in the lung interstitial (76). During infectious diseases, NAMs play an important role in preventing virus-related inflammation and tissue damage, while AMs play pro-inflammatory and anti-viral roles (77).

Additionally, during viral infections like influenza, NAMs inhibit IL-6 production. Since IL-6 contributes to severe inflammatory states and COVID-19 infection, thus, down-expression of this cytokine by the NAMs may be a checkpoint to regulate the hyper-inflammation, cytokine storm, in COVID-19 patients (76).

Interestingly, a study identified the unique macrophage subsets in the lungs of COVID-19 patients. In this study, the lung of patients with the milder disease was enriched with anti-inflammatory monocyte-derived (FCN1high) macrophages, while extremely inhabiting profibrotic (SPP1high) and inflammatory AM (FAPB4C) subsets in severe COVID-19 patients (77). The results show that the heterogeneity/polarization of macrophages and the relative amount of macrophage subtypes is a major factor in the severity of COVID-19. Alteration of macrophage's functional states by CoVs has been shown in previous studies. SARS-CoV-2 infection can manipulate macrophage's function to impair immunity (70). Infection of macrophages by MERS-CoV leads to an increase in the level of the major histocompatibility complex I (MHC I), CD80, and CD86 and the loss of expression of the major histocompatibility complex II (MHC II) (78, 79). Down-regulation of MHC II can disrupt normal immunological functions such as antigen presentation, B cells activation, and antibody production in COVID-19 patients (80-82).

Dendritic cells (DCs), as the primer effectors of antigen-specific immune responses, activate naïve T cells, initiate and regulate both specific T cell immunity and tolerance. DCs have an important

role in the innate immune responses to the kinds of infections and are the major linker between the innate and acquired immune systems(83).

Functionality, DCs are classified into two major populations: conventional/classical DCs (cDCs) ,or monocyte DCs, and the plasmacytoid DCs (pDCs). The precursor of both cDC and pDC may be common and both have been created from the same type of DC, also their maturation is mostly dependent on FMS-like tyrosine kinase 3 ligand (Flt3-L). cDCs or myeloid dendritic cells modulate pro-inflammatory responses, while plasmacytoid dendritic cells are responsible for fighting viral infections and by the production of type I interferons (IFNs-I) generate strong antiviral immunity (84). In addition to macrophages and further intensifying the cytokine storm, CoVs, especially SARSCoV- 2, are directly able to target, infect DCs frequency and functionally and diminish the production of antiviral cytokines via overexpressing inflammatory chemokines such as MIP- 1a(85, 86). SARS-CoVs also enhance the production of pro-inflammatory cytokines, including IL-6 and IL-12, by DCS and stimulate damaging inflammatory signals (87). The studies indicated that the number of both cDCs and pDCs was remarkably lower amongst the infected COVID-19 patients (88). Among these, pDCs are considered an important subset of DCs that can produce a high level of IFN I after encountering CoV, however, the role of pDCs in COVID-19 is not exactly known(89) .The evaluation of dendritic cells- related biomarkers suggested that accumulation, activation, and infiltration patterns for dendritic cells are affected during SARS-CoV-2 infection and severity of the infection are positively associated with dendritic cell deficiency. DC dysfunction can confuse and delay the immune system's response to SARS-CoV-2 infection and lead to a reduction of interferon secretion and a poorer prognosis of SARS-CoV-2 infection, thus suppressing T cell-dependent responses to SARS-CoV- 2. DCS deficiency may be a major contributor to disease progression and severity of infection, as suppression of DCS-induced T cell immunity impairs long-term humoral immunity and subsequently inhibits acquired immune responses related to CoV infection. The consequences of DCS reduction may even persist for a considerable time after recovery from COVID-19 and predispose the individuals to other pathogens and infections (90, 91). However, due to inadequate studies and the emergence of COVID-19, the exact and specific mechanisms by which the virus alters DC function remains unknown. Generally, disruption of the biomolecular signaling system is strongly associated with the level of inflammatory response experienced by a patient

- ***Trained Immunity***

The concept of ‘innate immune memory’’ or “trained immunity” refers to the non-specific and long-lasting eliciting/ amplifying of innate immune responses by whole microorganism vaccines and live-attenuated vaccines (LAV) such as measles, oral polio, bacillus Calmette-Guérin (BCG), influenza vaccine, or other microbial substances, which may provide cross-protective effects before, during and after the COVID-19 pandemic (92-94).

Trained innate immunity-induced pathways are not fully understood. In SARS-COV-2 infection, trained immunity via phenotypic changes, functional reprogramming, and durable epigenetic modifications in innate immune cell subtypes such as myeloid cells (monocytes, macrophages, and neutrophils), NK-cell, increasing the myelopoiesis, expression of PRRs and cytokine production (IFNs and IL-17) by T lymphocytes and enhances the number of cells migrating to the infection site (92, 95). Cross-reaction between myeloid cells, especially macrophages, and NK-cells and T cells promotes the production of pro-inflammatory cytokines, improves the quality, timely, and longevity of innate immune responses, and increases the host's nonspecific resistance to subsequent infections. Moreover, innate immune memory also occurs at the levels of progenitor stem cells of the bone marrow and epithelial cells.

Established trained immunity by the vaccines, limit the viral load, virus replication, and high transmission in the early stages of the disease, and leads to the boosted capacity of immune cell response to subsequent pathogenic encounters. However, the effectiveness of innate immunity responses is reduced with advancing age, the trained immunity using the heterologous effects of vaccination, promotes innate immune responses in the elderly population (96).

BCG, a live-attenuated vaccine (LAV) derived from *Mycobacterium bovis*, is the first line for the treatment of tuberculosis, a respiratory infectious disease, (97). In addition to the anti-tuberculosis properties of the BCG vaccine in children and anti-cancer properties in adults, which is now used in routine therapy of the early stages of bladder cancer, it by different mechanisms can reduce inflammation and infection within the alveolar space and protects the host against influenza pneumonia (98, 99) . The cross-protection effect of BCG against many bacterial and viral infections has been demonstrated in kinds of research (100). In emergencies and in cases where no specific vaccine is available, the BCG vaccine may, as a potential adjuvant, elicit a secondary innate

immune response against bacterial and viral pathogens to reduce respiratory and SARS-CoV-2 infections in a non-specific manner (97, 101). According to a study, vaccination of healthy individuals with BCG promotes the cross-talk between macrophages and NK cells augments cytokine production after ex vivo restimulation (102, 103)

Relief and improvement of respiratory tract infections and COVID-19 after BCG vaccination has been observed in several studies. One study showed that there were similarities between the amino acid sequences of the SARS-CoV-2 coating protein and the coating protein of different strains of Mycobacterium. This homology may provide effective immune responses by the BCG vaccine against SARS-CoV-2 infection.

It can be concluded that the BCG vaccine alone or in combination with other therapeutic agents, as an adjuvant, can be effective in reducing the severity of SARS-CoV-2 infection. Therefore, co-administration of BCG and SARS-CoV-2 vaccines may synergically enhance the efficacy, duration of immune responses in current and future SARS-CoV-2 specific vaccines, and may help to expand long-term immunological memory and reduce hospitalization during SARS-CoV-2 and other respiratory infections (104).

Evidence suggests that administration of BCG (oral or aerosol) using locally trained immune cells may lead to more effective and longer innate immune memory responses in the lungs of COVID-19 patients and mitigate sickness related to COVID-19 infection (101).

Types of research on the cross-protective effects of BCG vaccines against COVID-19 disease showed that BCG vaccines –induced trained immunity exhibit positive impacts on susceptibility to viral respiratory infections (105). Controlling the severity of COVID-19 infection by amplifying innate antiviral responses through trained immunity may be a durable approach (106).

Since the discovery, licensing and mass production of specific vaccines against COVID-19 is expensive and time-consuming and requires clinical and pre-clinical procedures, the use of approved and non-specific vaccines for trained immunity can be beneficial and effective. Because these vaccines have passed the initial clinical phases and only need a phase 3 trial of their efficacy and temporarily limit the spread of the pandemics until the development of specific COVID-19 vaccines (107). On the other hand, while some vaccines require the adjuvants in their formulation to increase effectiveness, BCG has potent “self-adjuvant” properties with several innate immune

sensors or PRRs, including TLRs (2,4,8), C-type lectin receptors Dectin-1, that enhance the active immunity of the vaccine (101, 106, 108, 109).

In addition, BCG vaccination might decrease the incidence of sickness and different respiratory bacterial, viral, and fungal infections during the COVID-19 pandemic, aiming to the reduction of long hospitalizations due to SARS-CoV-2 and other acute respiratory infections (101).

The findings show that the capacity and efficacy of vaccines in activating immunological memory is not only due to the stimulation of the lymphocyte response but also due to the induction of innate immune memory or trained immunity that provides readiness for innate immune cells against several pathogens.

- **Adaptive immunity**

The innate immune response, as the first line of defense, by releasing the cytokines, activate the acquired (adaptive) immune system, including humoral (B-lymphocytes) and cell-mediated (T-lymphocytes: both CD4+ helper T cells (Th) and CD8+ cytotoxic T cells (Tc)) immunity. Thus, innate reaction exposes the virus and directs the acquired response to control infection, but success lies in well-timed coordination between both immune responses.

The adaptive immune system has developed to supply more various and pathogen-specific defenses to recognize very delicate structures which involve in the formation of infectious agents. T cells are the main effectors of adaptive immunity that are differentiated into two sub-groups: TCD4+ and TCD8+ cells. CD4+ are helper T cells that by secretion of different cytokines, participate in the other immune cell's activation and excite humoral immune responses. The cytokines play important roles in the maturation, differentiation, and proliferation of B cells which produce plasma cells and antibodies to neutralize the pathogen. B cells are also differentiated into memory B cells to keep the body ready for the next exposure to a specific antigen. CD8+ cytotoxic T cells, directly eliminate the infectious agent and initiate cellular immune responses.

Although millions of people have recovered from COVID-19, there is still no credible evidence that how the adaptive immune system responds to the coronavirus. But over time, findings and information are being updated, and exact mechanisms will be discovered on how the immune system fights against the disease and the quality of responses. Understanding and paying attention to the qualitative characteristics of the responses will be crucial to improving the efficacy and

immunization of COVID-19 therapeutic approaches and SARS-CoV-2 vaccines. The number of T and B lymphocytes and the expression of other immune cells in severe cases and late stages are differentiated from mild cases and early stages of SARS-CoV-2 infection. The studies represented that in severe COVID-19 cases, both innate and adaptive immunity is ruined, while in mild cases is reduced lymphocyte proliferation and adaptive immunity, and innate immunity is conserved by the high expression of myeloid, activated dendritic cells, and NK cells and down-regulation of M2 phenotypes in monocyte subtypes. The evidence demonstrated that both phagocytic and T cells have an important role in the elimination of COVID-19 in both pre-clinical ad clinical models of infection. Therefore, it showed also that the cooperation of antibodies and phagocytic cells plays an important role in the eradication of coronavirus.

The findings demonstrated that the titers of SARS-CoV-2-specific antibodies in hospitalized COVID-19 are higher than in mild COVID-19 patients and healthy individuals. A high level of related antibodies is associated with COVID-19 severity (110, 111). As well, the increased level of antibodies can stimulate a range of Fc-dependent innate immune functions and high complement/antibody-mediated responses such as antibody-dependent cellular phagocytosis (ADCP),antibody-dependent complement deposition (ADCD), and antibody-dependent cell-mediated cytotoxicity (ADCC) in a manner linked to higher systemic inflammation. FC-dependent innate immune functions may have a dual function. On the one hand, it is beneficial in fighting viral infection by pathogens clearance, and on the other hand, it can be harmful to the body by stimulating the complement system,antibody-dependent inflammation (112, 113).

In normal conditions, when the adaptive immune system kills pathogens, a group of T and B cells is formed that have long-term memory and keep the body active and standby for the next exposure to the same pathogen. With the difference that next time the responses will be faster and stronger than before. In severe COVID-19 infection, infected people lose the memory of B and T cells and therefore do not have enough immunity against COVID-19 infection (114).

In COVID-19 patients, the production of inflammatory factors and specific infection markers is generally increased, which is positively related to the severity of the infection (115). Studies have shown that elevated serum levels of interleukin-6 (IL-6) aggravate the infection after 14-17 days of onset of symptoms (116, 117).

A study on the relationship between neutrophil to lymphocyte ratio (NLR) and the incidence of severe infection showed that SARS-CoV-2 infection can mainly affect the number of neutrophils and lymphocytes, especially T lymphocytes in the lungs, and cause pneumonia (infection and inflammation of the air sacs in the lungs) and lymphocytopenia (decrease in the number of lymphocytes) (118-120). These effects drastically enhance the expression of naive T helper cells and reduce memory T helper cells, also down-expressing natural killer (NK), dendritic cells, B cells, CD8+T, and HLA-DR-expressing cells in severe COVID-19 cases (115). All of these factors can contribute to severe pulmonary inflammation and the progression of infection.

Although the CD4+ T cells responses and antibodies production by B cells play a key role in the block the novel coronavirus infection (121). According to recent studies, antibodies do not play an effective role in long-term immunization against COVID-19 and are probably disappear after a few months (122). Indeed, antibodies dysfunction is compensated by T cells. T cells have a long-term memory for staying in the blood and play an important role in the host immune responses to COVID-19. Memory T cells from convalescent patients can target the virus by another invasion trick. It can be concluded that COVID-19 induces a strong memory T cell response, which can inhibit the recurrence of severe COVID-19 (121).

- ***Hybrid immunity ;(COVID-19 Infection + Vaccination= Hybrid Immunity)***

Recently vaccine scientists have proposed a theory called “hybrid immunity” or “super immunity’’ against SARS-CoV-2 infection. According to this theory, the combination of innate immunity and immunity created by a vaccine generates a much stronger immunization than an innate immunity and vaccine-produced immunity alone. In other words, vaccinating individuals who are previously infected with SARS-CoV-2 and recovered is likely to be more protective and safe against newer COVID-19 variants, particularly to variants of concern (VOCs) including delta and omicron variants, than vaccination in healthy people that resulting in a 25 to 100-fold increase in memory B cell-derived neutralizing antibodies than naturally (COVID-19 recovered patent)-induced immunity and healthy individuals vaccination alone (123-125). Interestingly, the potency and extent of vaccine-related neutralizing antibodies against a variety of variants were not predicted

in recovered individuals previously infected with SARS-CoV-2. The main reason for the breadth of neutralizing antibodies refers to memory B cells functions. Memory B cells extend the antibodies responses to re-infection in two ways: producing the same virus-specific antibodies and encoding the collection of antibodies mutations, which are mainly a repository of immunological variants (124-126).

Memory B cells are able to generate the antibodies that bind or neutralize VOCs, and the quality and efficacy of those memory B cells are increased over time. Therefore, the increase in neutralizing antibodies after vaccination of individuals previously infected with SARS-CoV-2 indicates the recall of diverse and high-quality memory cells after the main infection (125, 127). It seems that both B cell and T cell components participate in the hybrid immunity.

Cytokine storm

The immune system consists of both innate and acquired immunity, which is mainly regulated via chemotactic effectors named "cytokines". Cytokines differ in molecular weight, function, structure, secretion origin, as well as target cells, etc. Cytokines are produced by a wide range of immune cell types and can hire various immune cells such as monocytes, granulocytes, and lymphocytes that play a pivotal role in activating adaptive immunity. Depending on the disease and infection type, cytokine secretion levels are changed, leading to inflammation and clearance of pathogens (128, 129).

Following the binding virus to the alveolar epithelium and subsequent tissue damage and infection, SARS CoV- 2 infection employs the innate and adaptive immunity in an uncontrolled manner that fails the immune system to completely remove the virus. Studies have shown that rapid and alarming clinical reactions, as well as a high mortality risk in severe COVID-19, may be related to virus-activated cytokine storms (130, 131).

In stress or infectious conditions, ligand-receptor interactions stimulate the high production of immune cells, including natural killer cells (NKs), macrophages (Mϕs), dendritic cells (DCs), monocytes, B cells, and T cells that lead to the release of pro-inflammatory cytokines and activation of further white blood cells in a positive feedback loop. In infectious diseases, especially chronic infections, the production of cytokines is fluctuated and increased, which is known as "hypercytokinemia" or "cytokine storm" condition in the host, leading to cytokine release

syndrome (CRS) or macrophage activation syndrome (MAS) (116, 132). CRS and MAS occur in autoimmune disorders and are associated with excessive release of different cytokines and chemokines including IL-1β, IL-2, IL-6. IL-8, IL-10, IL-12, IL-17, IFN-γ, tumor necrosis factor-alpha (TNF-α),granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP-1), interferon gamma-induced protein 10 (IP-10), C-reactive proteins (CRP), CXCL10, D dimer, and ferritin, etc. Lymphopenia (low lymphocyte levels) and an increased neutrophil to lymphocyte ratio (NLR) may also occur during an infection crisis (133-135). The term "cytokine storm" (CS) was first described in 1993 in graft versus host disease (GVHD) (136, 137). CS, CRS, MAS can be developed directly by a wide range of infectious / non-infectious diseases including sepsis, organ transplantation, autoimmune diseases, as well as the side effects of monoclonal antibodies and specific drug regimens after immunotherapy treatments like chimeric antigen receptor (CAR) T cell therapy .Importantly, viral infections are one of the strong promoters of CS (138-141).

In SARS-CoV-2 infection, CS as an important symptom of COVID-19 disrupts the normal function of the immune system that manifesting as severe uncontrolled inflammation. Intensive care unit (ICU) patients show higher systemic levels of these inflammatory mediators compared with healthy and recovered individuals. It may be concluded that there may be a close relationship between CS level and COVID-19 severity (22, 142).

Although inflammatory responses play an essential role in the accumulation of proinflammatory factors and the elimination of pathogens, hyper-inflammatory states eventually convert into immune-suppressive and deleterious conditions. While T-helper 1 (Th1) responses to the inflammatory reactions are predominant in COVID-19 patients, cytokines including IL-4 and IL-10 can also be released from T-helper 2 (Th2) cells and suppress the inflammatory response (143)

Cytokine storms can create severe and adverse immunological reactions in COVID-19 patients, which is accompanied by the activation of more immune cells, including T helper 17 (Th17) of CD4 + lymphocytes. Th-17 cells express IL-17, IL-21, IL-22, and GM-CSF. IL-17 can stimulate the production of a wide range of proinflammatory cytokines and chemokines. Among cytokines, IL-17 is remarkably associated with lung injury, respiratory failure, cytokine release bursts, severe infection, and eventually, an increase in morbidity and mortality in COVID-19 patients. Therefore,

researchers have recommended that IL-17 and T helper 17 responses be targeted in the COVID-19 cytokine storm (137, 144).

Like cytokine storms in infectious and non-infectious diseases, the cytokine storm Covid-19 is composed of complex networks which might cross-talk with each other and disturb the natural and dynamic features of the network via connecting the SARS-CoV-2 spike protein to the related receptor, ACE2. This binding by hyperactivation of the complement system and other known and unknown specific pathways neutralizes the immunomodulatory responses and leads to overexpression of pivotal inflammatory factors such as IL-1 family, IL-6, IL-8, IL-10, TNF-α, interferon (IFN)-γ, TGF-β, NF-κB, and STATs (137, 145, 146).

The essential role of the IL-1 family (IL-1α / β) in T cell-related immunity, such as IL-2 expression and the IL-2 receptor (IL-2R), is unavoidable as a key orchestra in T cell homeostasis(147, 148).

In the acute phase of infection, IL-1α / β invokes immune cells to the site of infection and promotes the production of proinflammatory and specific cytokines to overcome viral infection. In IL-1α by triggering costimulatory signals on T $CD4^+$ cells, Th2 cells,(not on Th1 cells), stimulates Th2 immune responses which are essential in infection clearance. In hypersensitivity reactions, the deficiency of IL-1α/β is associated with a reduction in allergy symptoms (149).

Along with IFNs, IL-6 is another key inflammatory cytokine in the deterioration condition of COVID-19 and ICU patients. The percentage of IL-6 in severe COVID-19 patients and deceased individuals were more frequent than in mild COVID-19 patients (76 vs 30%) (150).

During viral SARS-CoV-2 infection, innate immunity stimulates infected cells to secrete cytotoxic cytokines such as interferons (IFNs) and diverse pro-inflammatory cytokines. IFNs warn and prepare the adjacent and uninfected cells for antiviral reactions and enhance the accumulation of proinflammatory cytokines of blood flow near infectious environment and activate phagocytes, macrophages, for removal of virus, as well as infected cells. . In chronic infection, excessive viral load delays the production of IFNS [11]. This delay makes the adaptive response incapable of fully fighting the infection. Postponement of IFN secretion leads to a storm of cytokine release (CRS), the severity of the infection, and uncontrolled inflammation. Depending on the specific receptor for different types of IFNs, interferons stimulate downstream signaling activation to trigger transcription factors and many IFN-activated genes that possess antiviral and immune-regulating /

boosting effects. Cytokine storm, as one of the important features of COVID-19 patients, is characterized by a decrease in type I and III interferons along with an increase in inflammatory chemokines and overexpression of IL-6. Cell and animal studies showed that delay in activation of IFN stimulated genes and initial type-I and III IFN responses to SARS-CoV-2 in the early stage and uncontrolled secretion of pro-inflammatory cytokines in the later stage of infection, leading to failure in timely immune response and severity of COVID-19 infection. (151-153).

Type II interferon (IFN-γ) is mainly produced by innate immune cells including phagocytes and natural killer (NK) cells, in reacting to viral and bacterial infections. IFN-γ is also generated by T helper (Th) CD4 and CD8 cytotoxic T lymphocyte (CTL) effector T cells during specific immune responses [35]. In COVID-19 infection, increased IFN-γ levels are directly related to the increment of virus loading and disease severity (154). In SARS-Cov-1 and MERS-Cov infections, elevated IFN-γ levels were associated with two signs of deterioration, pulmonary inflammation/ fibrosis, and broad lung destruction (56, 154, 155). In addition, IFN-γ has been introduced as a valid index of COVID-19 severity and ICU patients. Although the main source of IFN-γ production in COVID-19 patients is under discussion, it is widely believed that IFN-γ is directly produced by CD4 TH cells which enhances CD8 T cell differentiation and activates their cytotoxic function (56, 155, 156).

In addition, there is often an inverse relationship between fluctuations in T cell count and greater variability of cytokine concentrations in the peripheral blood of severe COVID-19 patients.

The cytokines also by activation of TCD4+ and TCD8+ lymphocytes of adaptive immunity, stimulate specific B cells -secreted neutralizing antibodies and cytotoxic T cells (also known as T_C, cytotoxic T lymphocyte (CTL)) to impede the spread of the virus and initiate programmed cell death (apoptosis) of viral laden cells (157).

According to studies, cytokine storms are divided into two main stages: The first stage is the delayed phase and the defect in the primary, temporary, and timely immune responses to an infectious agent that can seriously damage the body and worsen the clinical condition. This deficiency may be due to a possible genetic defect in the perforin and granzyme-associated pathways produced by natural killer cells (NK) and cytotoxic T lymphocytes. The next stage is the hyperactivity of the immune system to compensate for the previous failure, which is associated with the excessive production of

cytokines; and immunomodulators, corticosteroids, and cytokine receptor antagonists should be prescribed to prevent the severity of COVID-19 infection (158, 159).

Along with high serum levels of IL-6 and IL-2 receptor (IL-2R) in hyper-inflammatory responses and COVID-19 patients, the tumor necrosis factor-α (TNF-α) is a key cytokine that are participate in COVID- induced cytokine storm and has the dominant role in ICU patient's deterioration compared to non-ICU. TNF superfamily is mainly generated by different immune cells including macrophages, monocytes, neutrophils, endothelial cells, activated lymphocytes, etc. Depending on their receptors, they present pleiotropic effects with a variety of functions (22, 70, 155).

Noteworthy, TNF-α in the lungs of COVID-19 patients induces hyaluronan production by hyaluronan synthase-2 (HAS2) in the alveolar epithelium and endothelium of the lung and fibroblasts, which causes to flow and accumulate the fluid in the alveoli of the lungs, leads to hypoxia and ventilator admission (160, 161).

Increased TNF-α expression is the result of the interaction of macrophage-derived inflammatory factors with the lung epithelium. In conditions of CS and severe COVID-19 infection, lung macrophages may employ inflammatory monocytes and neutrophils to increase local inflammation to exacerbate CS at the systemic level. Interestingly, SARS-Cov-2 infection can induce TNF-α expression by lung epithelial cells as a result of CS (162).

In conclusion, higher plasma concentrations of IL-2, IL2R, IL-6, IL-7, IL-10, G-CSF, IP10, MCP1, MCP-3, IL-1ra, MIP1A, IFN-γ, and TNF-α in ICU patients Compared to non-ICU patients with COVID-19 suggested that cytokine storms are associated with disease severity and adverse outcomes. Failure of the immune response in the early stages of SARS-CoV-2 infection causes severe hyper inflammation of the lungs, leading to acute lung damage. CS is thought to be a severe immune reaction mediated by immune toxicity (131). Therefore, systemic medical approaches are needed to understand the interactions between the various elements of the complex network of the COVID-19 cytokine storm.

Results and Conclusion

Since the first human encounter with Covid-19, countless articles have been written on various aspects of the virus and its effects, as this crisis has had an unpredictable impact on global public health. As SARS-CoV-2 interacts with the immune system, copious inflammatory responses are

expressed that slow the progression of the disease in the body but in many cases can also cause death. This study examines the different types of immunity for COVID-19 and the distinct pathogenesis with separate additional explanations in more detail.

research results show that these viruses have four structural proteins covering E, M, N proteins, and S-Spike glycoprotein. According to the resultant studies, the four possible entry molecules (host cell receptor and host proteases) to facilitate the invasion of SARS-CoV-2 are the following points: (i) ACE2, (ii) TMPRSS2, TMPRSS4, and Furin (the host proteases), (iii) GPP78, and (iv) CD147. Initiation of innate immunity is mediated by pathogen-associated molecular patterns (PAMPs), which are recognized by some molecules name pattern recognition receptors (PRRs) encompassing five main families resulting in the introduction and production of cytokines and chemokines and eventually the death of the cell. Linkage of ligands to specific receptors induces the signaling pathways that stimulate the expression of transcription factors such as NF-kB, IRF3, and AP-1, which synergistically augment the type I interferon (IFN-I), (IFN-α, β) secretion.

CoVs by disturbance of pattern recognition receptor (PRR) signaling and TLR- induced signaling pathways create an inflammatory cascade that leads to cytokine storm and augments lung injury while inhibiting induction of interferons -antiviral responses. Elevated levels of pro-inflammatory cytokines and other inflammatory factors such as IL-2, IL-7, G-CSF, MCP-1, MIP-1a, IP-10, and TNF-a have been closely correlated with lymphopenia, abnormally low counts of lymphocytes, and more severe infection. Similar to SARS and MERS infection, cytokine storm and lymphopenia exhibit a pivotal role in the pathogenesis of COVID-19. In addition to manipulating cytokines, CoVs affect the function of innate immune executors such as neutrophils, Natural killer (NK) cells, Macrophages, and other immunological interactions including the capturing and presentation of antigens by professional APCs. Although the exact function of the immune response to SARS-CoV-2 is unknown and little information is available, observations suggest that elevated levels of proinflammatory cytokines called "cytokine storms" are due to the overactivity of myeloid cells associated with thrombosis, and vascular infiltration increases morbidity and mortality.

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Table. 1. Different mechanisms of pathogenesis of COVID-19 (host cell receptors and host proteases): (i) ACE2, (ii) TMPRSS2, TMPRSS4 and Furin (the host proteases), (iii) GPP78, and (iv) CD147

Figure. 1. Linkage of ligands to specific receptors induces the signaling pathways that stimulate the expression of transcription factors such as NF-kB, IRF3, and AP-1, which synergistically augment the type I interferon (IFN-I), (IFN-α, β) secretion

Figure. 2. Pro-inflammatory mediators summon the innate immune cells, including neutrophils and other myeloid cells, into the lung to excite potent local inflammatory responses.