Review Article

Immunity and Therapeutic Approaches against Coronavirus Disease 2019

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Abstract

The Coronavirus disease 19 (COVID-19) pandemic has resulted in considerable mortality and morbidity worldwide since identified in Wuhan in late 2019. It was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which is a causative agent of human respiratory tract infection. The detailed mechanism of host immune response and pathogenesis to this virus is not fully elucidated. In this review, we recapitulate the characteristics of immune pathogenies of SARS-CoV-2 infection based on the recent studies of SARS-CoV-2 and previous information on MERS-CoV and SARS-CoV infection that may contribute to disease severity and death. The pathogenesis of COVID-19 includes virus entry and replication, cellular and humoral immunity, cytokine storms, and immune evasion. We also discuss the current approved COVID-19 vaccines in Saudi Arabia; Pfizer-BioNTech (BNT162b2), Oxford-AstraZeneca (ChAdOx1 nCoV-19), and Moderna (mRNA-1273). Furthermore, we review the characteristics and the contraindication of vaccines, and the most effective clinical diagnosis for this virus to combat the infection of SARS-CoV-2.

Keywords: Immune response, Coronavirus, SARS-CoV, MERS-CoV, SARS-CoV-2, Vaccine

Introduction

Novel coronavirus disease 2019 (COVID-19), which is known as coronavirus-induced pneumonia, is a member of the family Coronavirdae named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019, this virus developed in Wuhan, a city in the Hubei Province of China, then the World Health Organization (WHO) announced the Public Health Emergency of International Concern (PHEIC) at the end of January 2020. On 11th March 2020, COVID-19 is considered a pandemic disease that shares about 80% sequence identity with SARS-CoV-1 [1]. Therefore, SARS-CoV-1, SARS-CoV-2, and Middle East respiratory syndrome CoV (MERS-CoV) are known as highly pathogenic human coronavirus infections that cause high mortality and morbidity [2, 3]. Up to date, there are about 577,429,314 confirmed cases of COVID-19 around the world of which 547,241,709 (94.77%) were cured, 6,407,868 (1.11%) were dead and the rest patients were either stable with about 23,779,737 (4.12%) or in critical situation 41,677 (0.01%). In Saudi Arabia, there are approximately 808,419 confirmed cases of coronavirus disease, 792,842 (98.07%) of the Saudi population recovered, while 9,243 (1.14%) of them were dead. Pneumonia appears to be the most common serious manifestation of COVID-19, characterized by fever, dry cough, fatigue, myalgia, dyspnea with acute respiratory distress syndrome (ARDS), and lymphopenia [4-6]. The cellular immune response is a crucial component of the immune defense that can recognize and control intracellular SARS-CoV-2 infection. However, an immunological role for orchestrated acute mortality from patients with SARS-CoV-2 is not yet illustrated. Therefore, the purpose of this review is to deliver an overview of the immune pathogenesis and T-cell response of SARS-CoV-2 infection, as well as, recent clinical diagnosis, treatment, and therapeutic/prophylactic vaccines against COVID-19, hinging on the information of two types of coronavirus; MERS and SARS that may assist in designing the appropriate immune intervention for.

Immune Pathogenesis of SARS-Cov-2 Infection

Immune function is considered a vital defense mechanism against infectious invasive pathogens. To facilitate the recognition of this new infection, the immunological mechanism of SARS-CoV-1 and MERS-CoV need to be addressed, especially changes in peripheral T-cells, their subsets, and B-cells. Coronaviruses classically infect the upper respiratory tract, however, MERS-CoV, SARS-CoV,

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and SARS-CoV-2 infect the lower respiratory tract and lead to pneumonia, which can be fatal.

Coronavirus is enveloped by single-stranded (ss), positive-sense RNA viruses' genome (26-32 kb). Two-thirds of the viral RNA open reading frame (ORF1a/b) encodes polyproteins that form the viral replicase transcriptase complex in MERS-CoV, SARS-CoV, and SARS-CoV-2. While, other ORFs on one-third of the genome encode four main structural proteins; spike (S), membrane (M), nucleocapsid (N), envelope (E), and other accessory proteins that do not participate in the replication of the virus [7] **(Figure 1)**. Coronavirus S-protein presents on the viral surface and this feature determines virus entry into the host cells-surface significantly, as angiotensin-converting enzyme 2 (ACE2) [8]. ACE2 is a receptor that binds to the envelope S glycoprotein of SARS-CoV-1 and SARS-CoV-2 [9, 10], dipeptidyl peptidase 4 (DPP4) for MERS-CoV, and CD209L for SARS-CoV [11]. This type I membrane protein (51), ACE2, are prone to viral infection by expressing on several cell types, such as heart, kidney, blood vessels, gastrointestinal tract, and lung alveolar type II epithelial cells [12]. After attachment to cellular receptor(s), enveloped SARS-CoV-1 requires membrane fusion to enter host cells at the plasma membrane [13]. Subsequently, the genomic RNA of the virus is released into the cytoplasm, then uncoated RNA is translated into two polyproteins, after which the sub-genomic RNA begins to transcript and replicate [7, 14]. As a result, these newly synthesized proteins insert into the endoplasmic reticulum (ER) membrane, and the Golgi apparatus and N are formed. Eventually, the newly formed virion is often seen inside vesicles, then fuses with the plasma membrane to secret it [3] **(Figure 2)**.

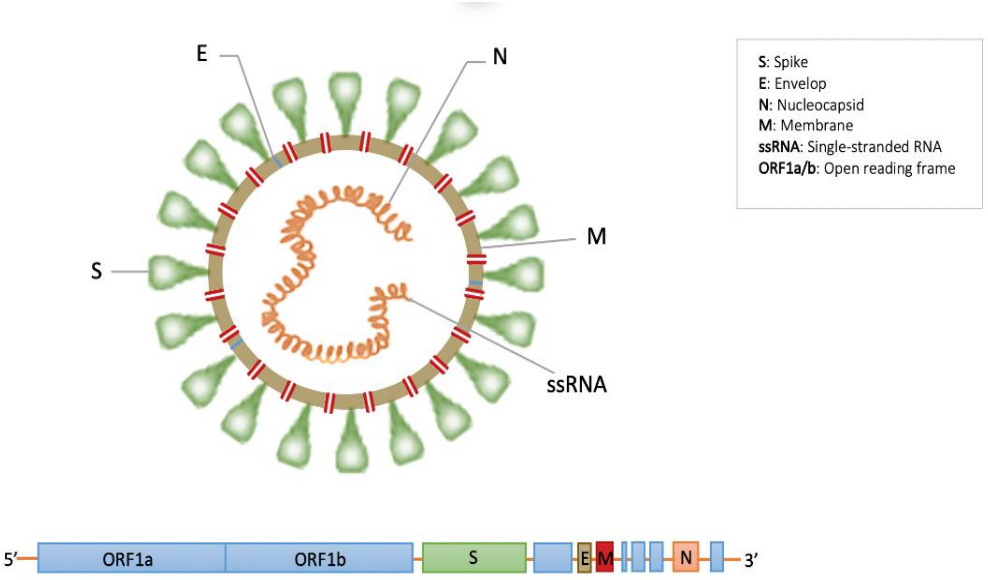

Figure 1. SARS-CoV-2 Structure and gene map. A. the structure of SARS-CoV-2 form enveloped with a positive single-stranded RNA (ssRNA) virus with a genome size (of 26-32 kb). In the SARS-CoV-2 gene map, the 5' terminal two-thirds of the genome open reading frame (ORF1a/b) encodes polyproteins, which form the viral replicase transcriptase complex. Other ORFs on one-third of the genome encode membrane (M), nucleocapsid (N), envelope (E), spike (S) protein, and other accessory proteins that do not contribute to virus replication.

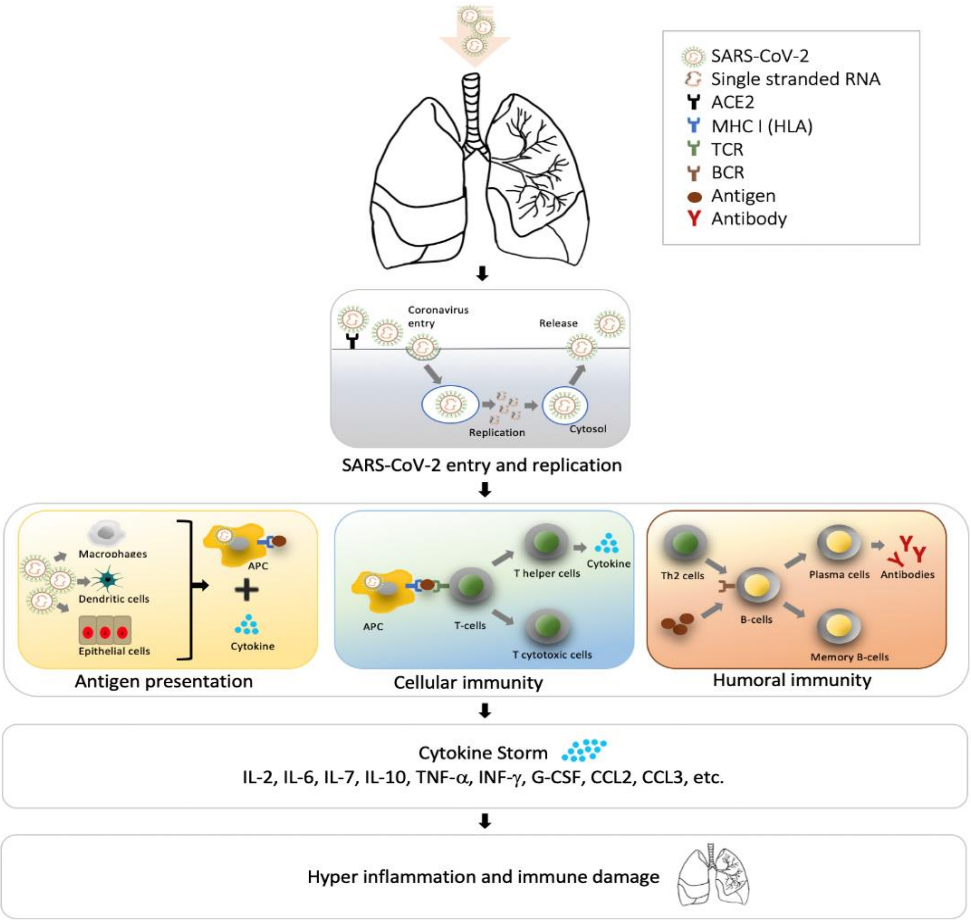

Figure 2. Immunopathogenesis of SARS-CoV-2 infection. Airborne transmission of SARS-CoV2 causes infection of angiotensin-converting enzyme 2 (ACE2) expressing on several cell types, (e.g. lung alveolar type II epithelial cells). After attachment, the virus's RNA is released into the cytoplasm and replicated. Hyperproduction of inflammatory cytokines is caused by the influx of monocytes/macrophages that is responsible for creating viral sepsis followed by lung injury. B-cells, CD4+, and CD8+ T-cells were reduced quickly in peripheral blood in the acute phase of SARS-CoV-2 infection. Antibodies, which are produced by B-cells, may assist neutralize SARS-CoV-2.

Subsequently, the inflammatory immune responses are activated and triggered after invading the cell by SARS-CoV-2 and completing its replication and proliferation cycle [15]. The virus antigens were coupled with antigen-presenting cells (APC], which play a central role in the induction of virus-specific innate immunity, inside the cells. Professional APC, including macrophage, dendritic cells (DC], and B-cells, a present antigenic peptide with human leucocyte antigen (HLA] in humans, or known as major histocompatibility complex (MHC], to virus-specific T-cells. Therefore, HLA class I and HLA class II contribute to the antigen presentation of the SARS-CoV infection [16, 17]. However, the antigen presentation of MERS-CoV mainly depends on the HLA class II, such as HLA-DRB1, and HLA-DQB1 [18]. Rapid detection of foreign pathogenic nucleic acids of coronavirus is caused by the expression of the cellular pattern-recognition receptors (PRRs) on DC, leading to the generation of interferon (IFN)-α and other types of IFNs [19, 20]. Several studies on COVID-19 demonstrated that acute organ tissue injuries are caused by hyperactivity of the innate immune system and the overproduction of inflammatory cytokines [21, 22]. Neutrophilia has been found in the respiratory tract of patients with COVID-19, leading to acute lung damage by demonstrating the neutrophils' toxicity and their degranulation [21, 23]. One of the main pieces of evidence that reveal the significant role of APC is the presence of interleukin (IL)-6, which is associated with DC and macrophages, and considered a destructive cytokine in severe clinical cases of COVID-19 [24, 25].

Accordingly, cellular and humoral immunity will be stimulated by a coronavirus. In cellular immunity, CD3+ T-cells were decreased rapidly in peripheral blood, as well as CD4+ and CD8+ T-cells in the acute phase of SARS-CoV-1 and SARS-CoV-2 infection [26]. However, the status of CD4+ and CD8+ T-cells was hyperactivated in COVID-19, as confirmed by high percentages of CD4 (3.5%) and CD8 (39.4%) double-positive fractions [27]. Xu, *et al*. [27] elucidate that hyperactivation of T-cells manifested by the upsurge of proinflammatory T helper (Th)17 in CD4 cells and

high cytotoxicity of CD8 cells is due to the severe immune injury in the COVID-19 patient. Additionally, Th17-cells are promptly shifted into pathogenic Th1 cells in the inflammatory site, then generate granulocyte-macrophage colony-stimulating factor (GM-CSF) by IL-1β and IL-12 to form a cascade signature of inflammatory CD14+CD16+ monocytes with high expression of IL-6 and IFN-γ [24, 28]. These activated immune cells may enter the pulmonary circulation, leading to immune damage to patients' lung function that may be associated with severe pulmonary syndrome or acute respiratory distress syndrome in COVID-19 patients [27, 29]. Therefore, the monoclonal antibodies that targeted the IL-6 receptor or GM-CSF may be effectively curbing or blocking immunopathology caused by SARS-CoV-2 to delay pulmonary immune injury [27, 29]. Furthermore, the memory CD4+ and CD8+ cells can persist for four years in recovered infected patients with SARS-CoV-1 and can perform proliferation of T-cells, IFN-γ production, and delayed-type hypersensitivity response. The response of specific Memory T-cells to the virus S peptide may still be recognized in 14 of 23 recovered patients from SARS-CoV after six years of infection [30]. Another study illustrated a similar effect of the specific CD8+ cells on MERS-CoV clearance in mice [31]. Zhou *et al*. [29] suggested that excessive activated immune response caused by pathogenic Th1-cells (GM-CSF) and inflammatory monocytes CD14+CD16+ could connect immunopathology of pulmonary causing deleterious clinical manifestation after infections of SARS-CoV-2, as we as acute mortality.

A recent study demonstrated that COVID-19 patients have elevated plasma concentrations of inflammation-related cytokines storm, which is an overproduction of immune cells and cytokines (IL-2, IL-7, IL-10, IFN-γ, granulocyte (G_CSF), tumor necrosis factor (TNF)-α, etc), and chemokines (monocyte chemoattractant protein (MCP)-1/CCL2, macrophage inflammatory protein (MIP)-1α/CCL3, etc) [5, 32]. Therefore, an inflammatory cytokine storm with lung immunopathological injury is caused by higher virus titers and dysregulated responses of cytokine/chemokine. The inflammatory storm may begin at one local site, then spread throughout the body through systemic circulation causing multiple organ failure, acute respiratory distress syndrome, and finally death in severe cases of coronavirus [33, 34].

Compared to cellular response, there are several types of research focusing on the humoral immunity of coronavirus. Th2 cells regulate humoral immunity by secreting cytokines such as IL-4, IL-6, and IL-10 and expressing the costimulatory molecule CD40L, which is bound to the CD40 receptor on B-cells to secret antibodies against virus/pathogen. B-cells decreased gradually in a patient with COVID-19 as the disease progressed and the antibodies profile has a typical pattern of IgG and IgM, as well as a reduction in T helper cells, T cytotoxic cells, natural killer cells, basophils, eosinophils, and monocytes [35]. An illustration of the immunopathogenesis of SARS-CoV-2 infection is shown in **Figure 2**. At the end of week 12, the SARS-specific IgM antibodies disappear, whereas the SARS-specific IgG antibodies are produced and increase steadily with the stage of the disease [36]. In another word, SARS-specific IgG antibodies, which are S- and N- specific antibodies, can last for a long time and play a protective function, thus the patient acquires the immune function after infection [36]. Recovering patients with SARS-CoV have sustained and high levels of S-protein-specific neutralizing antibody responses, which can be used to dictate the outcome of the disease [37]. It has been found that using a low dose of glucocorticoid in the early stage of severe acute respiratory syndrome for less than two weeks can control the severity [38]. Accordingly, the rational design of vaccines against COVID-19 needs to consider the prospect of antibody-driven pathology upon antigen re-challenge. MERS-CoV and SARS-CoV use numerous strategies to avoid the immune response for better survival in host cells. These coronaviruses can prompt the production of double-membrane vesicles that lack pattern recognition receptors (PRRs), then replicate in these vesicles, thereby avoiding the double-stranded (ds) RNA host detection [39]. PRRs are vital for the recognition of the evolutionarily conserved microbial structure called pathogen-associated molecular patterns (PAMPs). Although IFN-α and -β pathway is inhibited in infected mice with coronavirus, they have a protective effect on coronavirus infection [40, 41]. The induction of IFN may be blocked by ORFs protein of MERS-CoV through direct interaction with dsRNA. Besides, APC can be affected by MERS-CoV and SARS-CoV [7]. It is important to destroy the immune evasion of COVID-19 to develop a specific drug and treatment.

Current COVID-19 Vaccines

Effective COVID-19 vaccines are crucial for reducing the severity of disease, viral transmission, and shedding. The World Health Organization declared the launch of several SARS-CoV-2 vaccines in September 2020, to limit the mortality and morbidity from COVID-19 and to provide protection against coronavirus infection. Currently, there are three vaccines approved in Saudi Arabia against COVID-19; Pfizer-BioNTech (BNT162b2), Oxford-AstraZeneca (ChAdOx1 nCoV-19), and Moderna (mRNA-1273). Pfizer-BioNTech and Moderna vaccines were developed using mRNA, while AstraZeneca was developed using the adenovirus vectored COVID-19 vaccine [42]. Vaccines went through 3 phases in Saudi Arabia soon after being developed; Phase one targeted healthcare workers and individuals over 65 years old, then the next phase targeted healthcare practitioners and people over 50 years old. All residents and citizens were targeted in the last phase (3) in Saudi Arabia [43].

Pfizer-BioNTech

BNT162b2 is one of the highly purified single-stranded, 5-capped mRNA produced by cell-free *in vitro* transcription from the corresponding template of DNA that encodes the S protein of COVID-19 to produce a safe protein that prompts neutralizing antibody and cellular immune responses. The

nucleoside-modified mRNA in this vaccine is formulated in a lipid nanoparticle that is injected intramuscularly (IM) into the human body. Then, it inserts its mRNA into the cytoplasm once attached to the host cells to permit expression of the viral S antigen and T helper cells, which produce cytokines (e.g. IL-2, IL-4, and IL-5), leading to producing a huge amount of antibodies that can neutralize and destroy the virus [44]. Furthermore, IL-2, IL-4, and IL-5 stimulate the T cells to proliferate the memory T cells and destroy the infected cells. This vaccine is indicated for active immunization of individuals from 5 years old and older. The dosage for primary doses of pediatrics 5-11 years old is 0.2 mL, while it is 0.3 mL for individuals ≥12 years old. It has been reported that the BNT162b2 vaccine was 95% effective against COVID-19 by reducing infection, hospitalization, severe disease, and death [42, 44].

Oxford-AstraZeneca (ChAdOx1 nCoV-19)

ChAdOx1 of-19 is a product using a replication-deficient chimpanzee adenovirus vector encoding S glycoprotein of SARS-CoV-2 that is produced in genetically modified human embryonic kidney 293 cells. This protein is expressed locally stimulating an immune response. This vaccine is approved for individuals 18 years old and older (≥ 18 years old), and the efficiency of the vaccine is 76% at preventing symptomatic SARS-CoV-2 [42, 44].

Moderna (mRNA-1273)

Moderna (1273) uses lipid nanoparticles with a formulated mRNA vaccine as mentioned in the Pfizer-BioNTech vaccine. Genetically engineered RNA or DNA was used as a cutting-edge approach to generate S protein to safely prompt an immune response. This vaccine can elicit both neutralizing antibodies and cellular immune responses to the S protein antigen that may protect the human body against SARS-CoV-2. Moderna vaccine is indicated for active immunization of individuals from 12 years old and older (≥12 years old). The efficacy of this vaccine is estimated at 94% against COVID-19 [42, 44].

All these COVID-19 vaccines were approved for their effectiveness against COVID-19 disease, however, there are several adverse effects present in individuals at various ages including, pain or swelling at the site of injection, headache, fatigue, muscle and joint pain, chills, fever, nausea, malaise, lymphadenopathy, and anaphylaxis. It has been reported that anaphylaxis is one of the complications that rarely happens after COVID-19 vaccines, but it was reported by the Vaccine Adverse Event Reporting System after the first dose of the Pfizer-BioNTech vaccine [44, 45]. Rare cases of thromboembolic events, blood clots, pulmonary embolism, and thrombocytopenia were reported after the Oxford-AstraZeneca vaccine. It has been reported that rare cases present with Bell's Palsy (facial paralysis) following the Moderna vaccine [44]. Hence, hypersensitivity to the active substance of thesis vaccines needs to be considered and reviewed by the exemption committee at the ministry of health. The use of these vaccines should be following official guidance, as stated by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). **Table 1** demonstrates a summary of COVID-19 vaccine characteristics.

Table 1. Summary of approved COVID-19 vaccines in Saudi Arabia

	Pfizer-BioNTech		Oxford-AstraZeneca	Moderna
Age group	5-11years old	≥12 years old	≥18 years old	≥12 years old
Mechanism of action	mRNA		Adenovirus viral vector	mRNA
Antigen	Full-length S protein		S protein	Full-length S protein
Number of doses	2		2	2
Interval between doses	21 days		21 days	21 days
Approved Boosters	N/A	1st and 2nd boosters' doses	N/A	1st and 2nd boosters' doses
The age group of boosters	N/A	≥ 50 years old or immunocompromised for ≥ 16 years old	N/A	≥ 50 years old or immunocompromised for ≥ 16 years old
The interval between doses and 1st boosters	N/A	90 days	N/A	90 days
The interval between two boosters	N/A	120 days	N/A	120 days
Administration	Intramuscular (IM)	Intramuscular (IM)	Intramuscular (IM)	Intramuscular (IM)
Overall efficacy	95% of disease		76% for disease	94% of disease

Special groups				
Pregnancy	N/A	Yes	Yes	Yes
Breastfeeding	N/A	Yes	Yes	Yes
Age (12-18 years old)	N/A	Yes	N/A	Yes
Immunocompromised	Yes	Yes	Yes	Yes
Contraindications				
Hypersensitivity after the first dose	Need to contact MOH and to be reviewed by the committee of exemption			
Hypersensitivity to food or medications	Need to extend the observation period to 30 minutes			
Bleeding disorders or taking anticoagulant medication	Need to extend the observation period to 30 minutes			
Unwell with fever or Acute illness	Need to differentiate the vaccine till symptoms are resolved.			

Clinical Diagnosis of COVID-19

Epidemiological history, clinical manifestations, and some auxiliary examinations are important in SARS-CoV-2 clinical diagnosis. Auxiliary examinations comprise CT scan, nucleic acid detection, and immune identification technology that targets viral antibodies or antigens (enzyme-linked immunosorbent assay (ELIZA) and point of care testing (POCT) of IgM/IgG), and blood culture. CT scan is a more sensitive test for early detection of SARS-CoV-2 infection and evaluation of COVID-19 severity. Real-time quantitative polymerase chain reaction (RT-qPCR) and high throughput sequencing are the two frequently used nucleic acid detection technologies [7]. RT-qPCR is a very accurate, effective, and straightforward method for detecting the genetic material of SARS-CoV-2 in blood and respiratory secretions [46]. In addition, ELISA and POCT of IgM/IgG kits for COVID-19 have been developed and have revealed a higher detection rate than nucleic acid technology. The antibody can be detected in saliva samples using ELISA with a specificity of 100% and sensitivity of 84.2% in a general symptomatic individual (n=149 samples) [47]. The antigen test is an effective and fast COVID-19 rapid test that is used by using respiratory secretions and providing results within 15 minutes. This test utilizes membrane technology based on lipid nanoparticles and monoclonal antibodies directed against the nucleoprotein antigen of the virus [48].

Conclusion

In this review, the immune pathogenesis, drug development, and an effective clinical diagnosis of COVID-19 have been discussed based on the information from research on SARS-CoV and MERS-CoV, as well as, ongoing SARS-CoV-2 studies. The occurrence and development of COVID-19 depend on the interaction between the individual's immune system factors (e.g. genetic, gender, age, etc) and the viral factors (e.g. virus type, mutation, viral titer, etc). All these factors underlying immune dysregulation in severe SARS-CoV-2 contribute to understanding the pathogenesis of COVID-19, the reinfection reason, the severity and the duration of the COVID-19 disease, and identifying strategies for targeting medical interventions. Additional studies are needed to clarify the correlation between antibody titer and protection against COVID-19 reinfection, and the risk of SARS-CoV-2 vaccinations also should not be ignored.

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