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Review Article

Immune response in COVID-19: A review

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ABSTRACT

The immune system protects against viruses and diseases and produces antibodies to kill pathogens. This review presents a brief overview of the immune system regarding its protection of the human body from COVID-19; illustrates the process of the immune system, how it works, and its mechanism to fight virus; and presents information on the most recent COVID-19 treatments and experimental data. Various types of potential challenges for the immunes system are also discussed. At the end of the article, foods to consume and avoid are suggested, and physical exercise is encouraged. This article can be used worldwide as a state of the art in this critical moment for promising alternative solutions related to surviving the coronavirus.

Contents

Introduction

The earth is relaxing but humans are dying. As of April 18, 2020, more than 154,000 have people died, 2.2 million have been affected, and at least 185 countries have been affected by the coronavirus. The world experienced coronavirus for the first time in 2002–2003 through severe acute respiratory syndrome (SARS), and in 2011, Middle East respiratory syndrome (MERS) for the first time. The causative agents for both cases (SARS-CoV and MERS-CoV,) were

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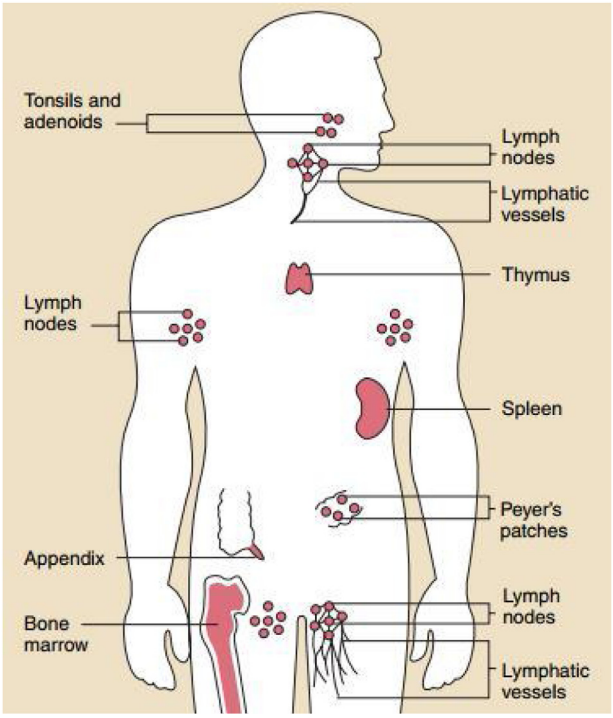

Fig. 1. The organs of the immune system are positioned throughout the body [12].

newly identified coronaviruses of zoonotic origin in the genus Beta coronavirus [1]. The present coronavirus (SARS-CoV-2) COVID-19 appeared for the first time in Wuhan, China, at the end of 2019. People are being affected by human-to-human transmission due to close contact [2,3], and people affected by COVID-19 suffer from severe respiratory illness [4]. People who are elderly and have many comorbidities are the most vulnerable to COVID-19 [5,6].

There is no registered treatment or vaccine for this disease [7]. For the treatment of affected people, limited urgent use of chloroquine and hydroxychloroquine have been approved by the United States Food and Drug Administration. The use of an antiviral drug called Favilavir as a treatment for coronavirus has been approved by the National Medical Products Administration of China. The drug has shown efficacy in treating the disease, with very low side effects in a clinical trial involving 70 patients. The clinical trial has been ongoing in Shenzhen, Guangdong province [8]. This review article reported the recent observations regarding the development of the immunity level in the human body for resisting the coronavirus as an alternative solution before the invention of drugs and vaccinations.

Process of the immune system in the human body

The body contains the organs of the immune system (Fig. 1), which protects against diseases [9,10]. It plays a key role to maintain health and pathogenesis. It also protects the body from harmful substances, germs, and cell changes (neoplasm) [11]. The key player in the immune system is the white blood cells, which can travel throughout the body through the blood vessels. To monitor for invading microbes, the body exchanges cells and fluids between blood and lymphatic vessels and enables the lymphatic system. The lymphatic vessels carry lymph. Each lymph node contains specialized compartments where they can encounter antigens. Through the incoming lymphatic vessels, the immune cells and foreign particles enter the lymph nodes. When they are in the bloodstream, they are transported to tissues throughout the body. They continue the cycle all over by patrolling for foreign antigens everywhere and then gradually drift back into the lymphatic system. The immune cells gather, work, and serve to confront antigens in lymph nodes and the spleen's compartments [12].

Impacts of Covid-19 on the human body

COVID-19 is an RNA virus with a crown-like appearance. Its diameter is approximately 60–140 nm. On one side, it has a concave surface with a ridge. It makes a larger binding interface, as well as more contacts with ACE2. It can make better contact with the N-terminal helix of ACE2 and have higher affinity [13]. It is transmitted through respiratory droplets from coughing and sneezing and enters the nasal system by inhaling and starts replicating. ACE2 is the main receptor for the COVID-19 virus [14]. The spike protein (S protein) present on the surface of COVID-19 is pinched inside the host cell binding to the ACE2 receptor. Here, the enzyme furin is present in the host cell and plays a vital role for the virus to enter, which was absent in SARS-CoV [15]. Next, the virus starts to propagate with limited innate immune response and can be detected by nasal swabs. The virus then propagates and reaches the respiratory tract, where it faces a more robust innate immune response. At this stage, the disease is clinically manifest and an innate response cytokine may be predictive of the subsequent clinical course [16]. For beta and lambda infections, viral-infected epithelial cells are a major source [17]. The disease will be mild for 80% of the infected patients and mostly restricted to the upper and conducting airways [18]. With conservative symptomatic therapy, these individuals may be monitored and monitored at home. Approximately 20% of the infected patients develop pulmonary infiltrates and some of these develop very severe disease [19]. The mortality rate of severe patients with COVID-19 can be as high as 49%, based on a recent epidemiological by China CDC [20]. In Wuhan, 292 patients with COVID-19 were studied. Age was the risk factor of patients with a severe condition, as shown by the Lasso algorithm. When the age of patients with a severe condition increased by 5 years, the risk increased by 15.15%. Most of the patients with COVD-19 were elderly patients in the severe group, with basic diseases. Chronic obstructive pulmonary disease, hypertension, malignant tumor, coronary heart disease, and chronic kidney disease were more frequent in the severe group than in the mild group. Of 145 severe cases, 51 patients died (34.69%), and 90.2% of the patients who dies were over 60 years old. Forty patients had basic disease out of 51 deaths (78.43%). Reports have demonstrated that patients aged older than 60 years who have comorbidities, especially hypertension, are at risk for severe disease and death from SARS-CoV-2 infection [21–23].

Mechanism of immune systems in the human body against COVID-19

Because there is no registered medicine or vaccine against COVID-19, the immune system is the best defense because it supports the body's natural ability to defend against pathogens (eg, viruses, bacteria, fungi, protozoan, and worms [24,25]) and resists infections. As long as the immune system is functioning normally, infections such as COVID-19 go unnoticed. The three types of immunity are innate immunity (rapid response), adaptive immunity (slow response), and passive immunity (Fig. 2). Passive immunity has two types: natural immunity, received from the maternal side, and artificial immunity, received from medicine. Skin and inflammatory responses begin when the body is affected [26,27]. However, when the body encounters germs or viruses for the first time, the immune system cannot work properly, and illness can occur. This scenario is what has occurred in the case of COVID-19 [28].

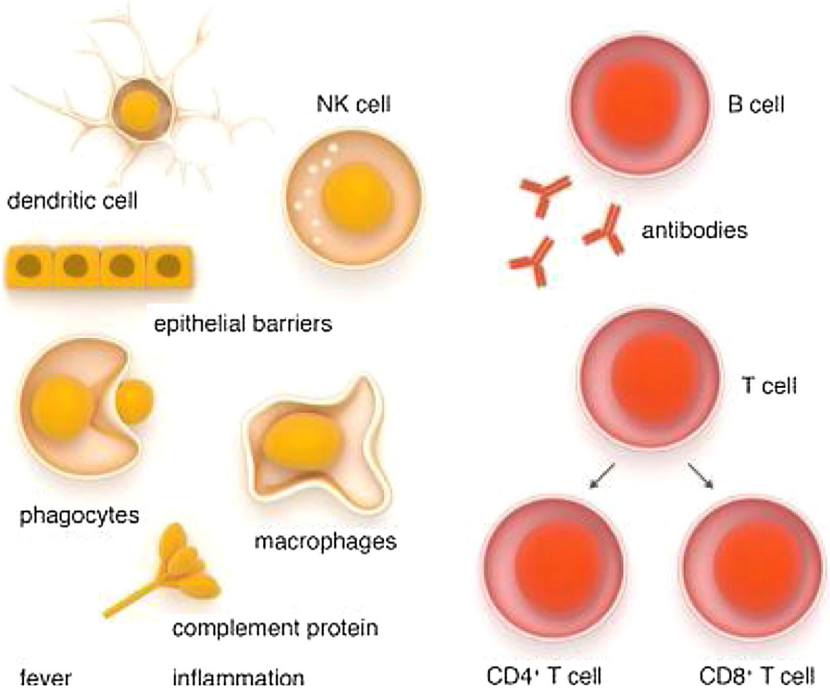

Fig. 2. Innate and adaptive immune system [28].

When the cells of the immune system become educated, they complete their jobs by recirculating between central and peripheral lymphoid organs and migrating it and from sites of injury via blood (Fig. 3). Blood carries naïve and educated immune cells from one site to another, as it flows throughout the body, and acts as a pipeline for the immune system. The cells again enter into the bloodstream to be transported to tissues throughout the body after exiting these nodes through outgoing lymphatic vessels [29].

Many molecular and cellular profiling assays are now available for the study of the human immune system (Fig. 4). The level of advancement of instruments has increased (e.g., polychromatic flow cytometers have improved). In the fields of genomics and proteomics, major technological breakthroughs have also occurred, creating a unique facility for the study of human beings in health and disease where inherent heterogeneity dictates that large collections of samples be analyzed [29].

After being affected by virus immune responses to mediate antibody. The B cells are assisted by T cells to differentiate into plasma cells, which then produce antibodies specific to a viral antigen. A neutralizing nature antibody is efficient in fully blocking the virus from entering into host cells to limit the infection and plays a very intense protective role at the later stage of infection and prevents relapse of infection. By contrast, a cellular immunity response can be observed inside the infected cells, which is mediated by T-lymphocytes. The overall adaptive immune response is directed by helper T cells, and cytotoxic T cells play a vital role in the clearance and cleaning of viral-infected cells [30].

Information from SARS-CoV and MERS-CoV may allow the exploration of knowledge to understand how SARS-CoV-2 escapes the host's immune response, because data on SARS-CoV-2 remain limited. Notably, 80% of the RNA sequence of SARS-CoV and 50% of the RNA sequence of MERS-CoV match the RNA of SARS-CoV-2 [31], and SARS-CoV-2 exhibits additional genomic regions. Compared with SARS-CoV and other closely related coronaviruses, its S protein is 20–30 amino acids longer. Thus, SARS-CoV-2 has similar immune evasion strategies, but an additional mechanism remains undiscovered [32,33].

The synopsis of Shi et al. [34] is based on clinical common sense. They proposed some normal approaches for the treatment of patients with COVID-19 (Fig. 5). They posited that the two-phase immune defense-based protective phase and inflammation-driven damaging phase division are essential. In the first phase, doctors should attempt to boost immune response, and in the second phase, they should attempt to suppress it. Vitamin B3 should be used immediately after the coughing begins because it is highly lung protective. When breathing difficulty starts, hyaluronidase can be given intratracheally and simultaneously, 4-MU can be used to inhibit HAS2. Clearly, susceptibility information will be provided by HLA typing for strategizing prevention, treatment, vaccination, and clinical approaches.

Reasons for failure

The leading cause for mortality of patients with COVID-19 is respiratory failure from acute respiratory distress syndrome [35]. Secondary hemophagocytic lymphohistiocytosis (sHLH) is characterized by fulminant and fatal hypercytokinemia with multiorgan failure, and it is underrecognized. Viral infection triggers sHLH and occurs in 3.7%–4.3% of sepsis cases in adults [36,37]. sHLH, resembled by a cytokine profile, is associated with COVID-19 disease severity, characterized by increased interleukin (IL)-2, IL-7, interferon-inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-, monocyte chemoattractant protein 1, and tumor necrosis factor- (TNF-) [38]. A recent retrospective fatality predictor's multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin and IL-6, suggesting that mortality might due to virally driven hyperinflammation [39].

Treatment for patients with COVID-19

Research is ongoing worldwide to develop a vaccine against COVID-19. According to a report [40], 115 vaccine candidates are

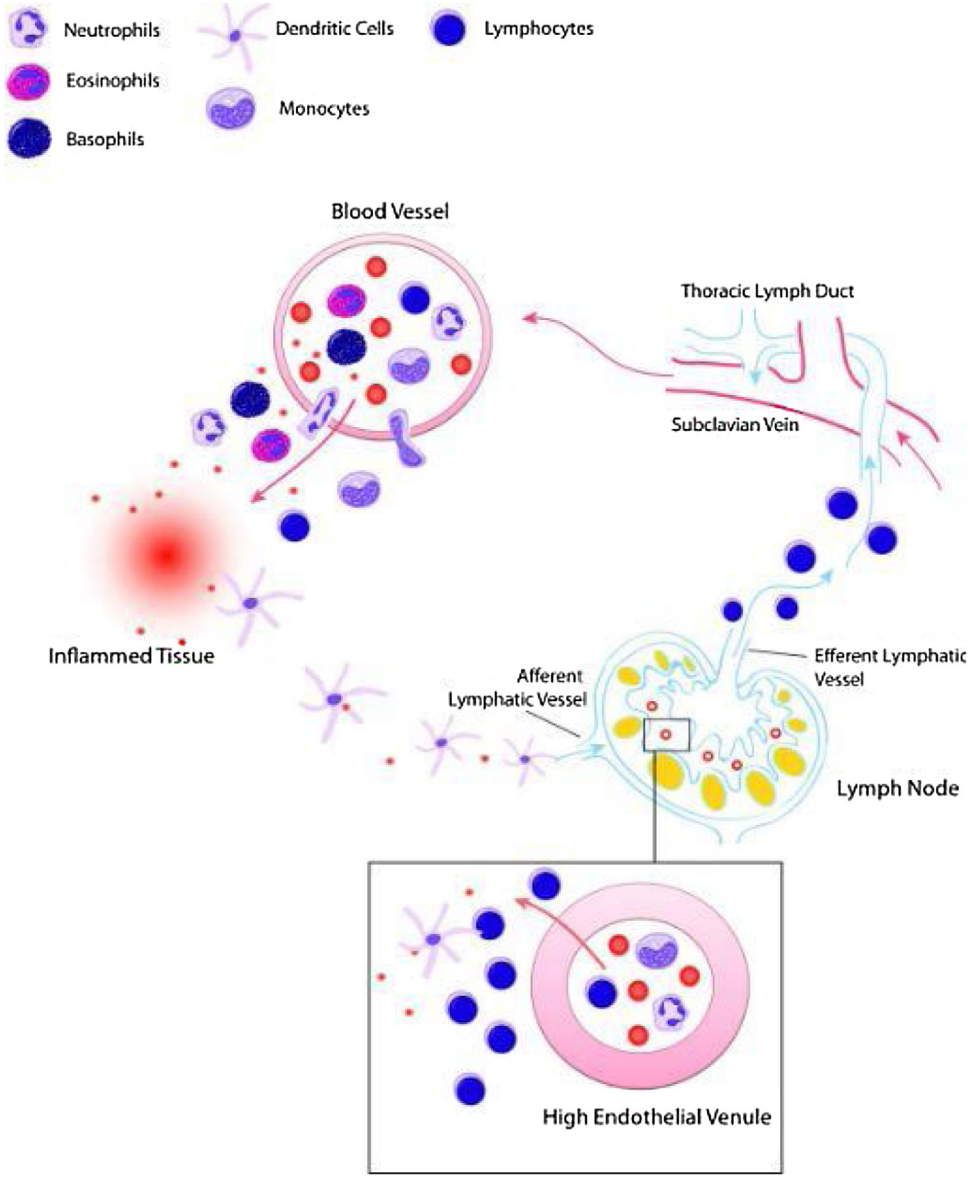

Fig. 3. Blood in the pipeline of the immune system [29].

Table 1
Clinical phase vaccine candidates for COVID-19 [40].

Candidate	Vaccine characteristic	Lead developer	status
mRNA-1273	LNP-encapsulated mRNA vaccine encoding S protein	Moderna	Phase I (NCT04283461)
Ad5-nCoV	Adenovirus type 5 vector that expresses S protein	CanSino Biologicals	Phase I (NCT04313127)
INO-4800	DNA plasmid encoding S protein delivered by electroporation	Inovio Pharmaceuticals	Phase I (NCT04336410)
LV-SMENP-DC	DCs modified with the lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	Shenzhen Geno-Immune Medical Institute	Phase I (NCT04276896)
Pathogen-specific aAPC	aAPCs modified with the lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Shenzhen Geno-Immune Medical Institute	Phase I (NCT04299724)

being developed. Among them, 78 are confirmed as active and 37 are unconfirmed; 73 are in exploratory out of 78 confirmed active projects. The most advanced candidates have been moved into clinical development. Table 1 shows the clinical phase vaccine candidates for COVID-19.

According to another report [41], 108 adults have received a low, middle, or high dose of the vaccine, given as an intramuscular injection. All those adults were not affected by SARS-CoV-2, and their age was in between 18 and 90 years. Their mean age was 36.3, and 51% of them were male and observed for 28 days. Live

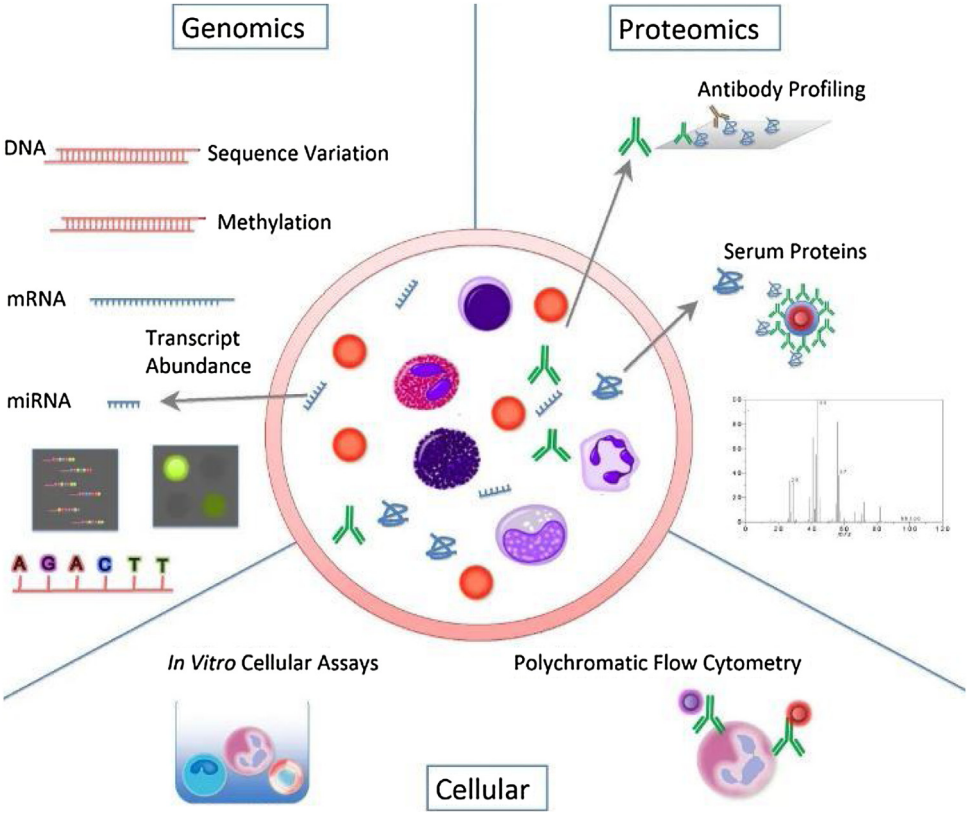

Fig. 4. Immune profiling armamentarium [29].

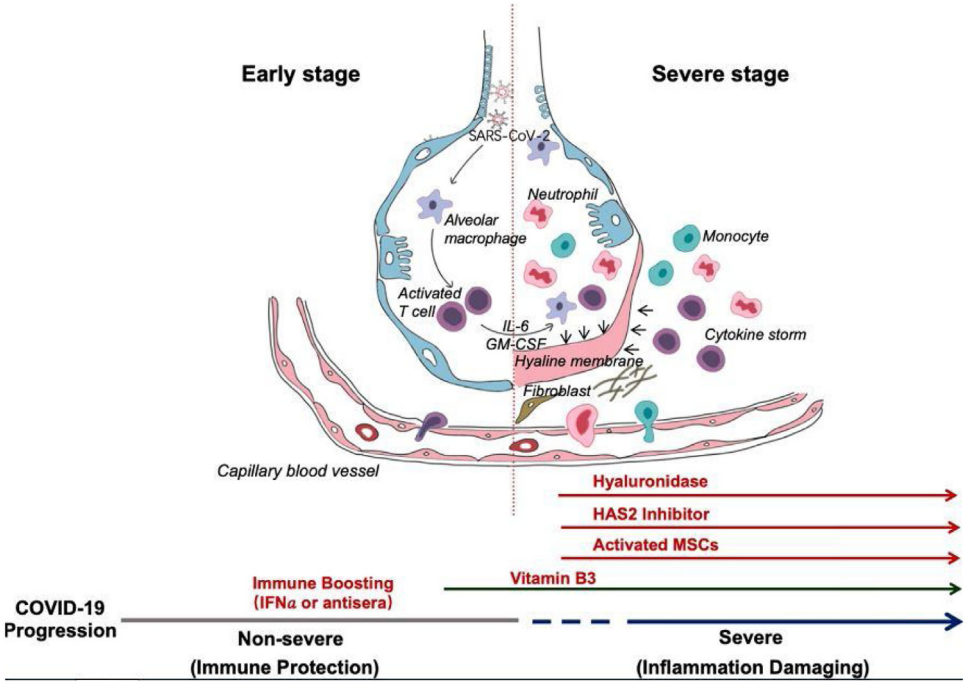

Fig. 5. Progression of COVID-19 infection and potential adjuvant interventions [34].

virus or pseudovirus neutralization assays can detect neutralizing antibodies, in addition to binding antibodies measured by ELISA at approximately 14 days.

At 28 days, dose-dependent antibody responses peaked, with seroconversion documented in 50%–75% of the participants in the middle- and high-dose groups. Moreover, specific T cell responses toward the spike glycoprotein were shown by interferon enzyme-linked immunospot and flow-cytometry. Among 83%–97% of participants, dose-dependent responses were detectable starting from 14 days. The most common adverse effects were fever, fatigue, headache, and muscle pain. One study demonstrated that [42] for the treatment of COVID-19, convalescent plasma therapy is effec-

Table 2
Associated adverse events to convalescent plasma in different epidemics.

Country	Viral etiology	Adverse events	References
China	COVID-19	None	[47]
China	COVID-19	None	[48]
China	COVID-19	Self-limited facial erythema in 2/10 patients. No major adverse events.	[49]
China	COVID-19	None	[50]
South Korea	COVID-19	None	[51]
China	SARS-CoV	None	[52]
China	SARS-CoV	None	[53]
China	SARS-CoV	None	[54]
Taiwan	SARS-CoV	None	[55]
China	SARS-CoV	None	[56]
China	SARS-CoV	None	[57]
China	SARS-CoV	None	[58]
South Korea	MERS-CoV	None	[59]
Guinea	Ebola	Nausea, skin erythema, fever. No major adverse events.	[60]
China	Influenza A (H1N1)	None	[61]
China	Influenza A (H1N1)	None	[62]
China	Influenza A (H1N1)	None	[63]
China	Influenza A (H1N1)	None	[64]

Table 3
Off-label drugs against SARS-CoV-2 and COVID-19 disease [92].

Drug	Class	Target	Dosage	References
Camostat mesilate	Serine protease inhibitor	TMPRSS2	200 mg three times daily, for 2 weeks, per oral	[73,74]
Nafamostat mesilate	Serine protease inhibitor	TMPRSS2	240 mg daily, for 5 days, per oral	[75]
Chloroquine phosphate	Antimalarial drug	ACE2	250 mg daily until clinical convalescence, per oral	[78,79]
Hydroxychloroquine	Antimalarial drug	Endosome, pH elevation	400 mg loading dose twice daily at day 1, 200 mg twice daily for 4 days, or 600 mg for 6 days, or 400 mg for 5 days, per oral	[80–82]
Remdesivir	Antiviral drug	RdRp	200 mg loading dose at day 1, 100 mg for 9–13 days, per oral or intravenous	[83–85]
Lopinavir/ritonavir	Antiviral drug	Viral proteases	400 mg lopinavir and 100 mg ritonavir twice daily, for 14 days, per oral	[86–88]
Umifenovir	Antiviral drug	Membrane fusion, clathrin-mediated endocytosis	400 mg three times daily, for 9 days, per oral	[89,90]
Favipiravir	Antiviral drug	RdRp	6000 mg loading dose at day 1, 2, 400 mg for days 2–10, per oral	[91]

tive. The survival rate of patients with SARS of viral etiology has been improved with this treatment [43]. Pre-donation assessment is performed to ensure compliance with the current regulations for plasma donors [44]. Individuals aged between 18 and 65 years who have recovered and not been infected by COVID-19 for the last 14 days are the convalescent donors. Individuals from the tropical disease areas were also excluded. Plasma, approximately 400–800 mL, was collected from each donor, stored in units of 200 or 250 mL, and frozen within 24 h of collection to be used for further transfusions [45]. The safety of using convalescent plasma is another issue. Any adverse event did not associate during the epidemic of influenza, SARS-CoV, and MARS-CoV but did occur for Ebola. Reports say treatment with convalescent plasma for patients with COVID-19 is safe without any major adverse events [46]. Table 2 shows the associated adverse events to convalescent plasma in different epidemics.

Because there is no definite and specific treatment for patients with COVID-19, some antiviral agents are prescribed to the patients, depending on their condition and location. Among the antiviral agents, remdesivir is the most well-known potential drug for the treatment of patients with COVID-19. For the treatment of Ebola virus infection in 2017, Gilead Sciences synthesized and developed remdesivir, and it is a phosphoramidate prodrug of an adenosine C-nucleoside and a broad spectrum antiviral agent [65].

Hydroxychloroquine and chloroquine are other drugs that have a long history of clinical use and similar chemical structures and are often used for the treatment of malaria erythematosus and rheumatoid arthritis [66]. Lopinavir is another drug, which was administered and marketed in combination with ritonavir by Abbott under the brand name Kaletra in 2000. Lopinavir is a protease inhibitor with high specificity with HIV-1 protease [67]. Another drug, umifenovir, was first developed in Russia and used in Russia and China for the treatment of prophylaxis, infections associated with influenza A and B, and other arbovirus [68]. Favipiravir was developed by Fujifilm Toyama Chemical, Japan, in 2014, for treating avian influenza resistant to neuraminidase inhibitors [69]. Oseltamivir is used to treat influenza A and B. This drug targets the neuraminidase distributed on the surface of the influenza virus to inhibit the spread of the influenza virus in the human body [70–72]. Table 3 presents the off-label drugs against SARS-CoV-2 and COVID-19.

Recent observations of COVID-19 treatment improving the immune system: case study

Researchers are attempting to improve the immune system against COVID-19 and here some of the data reviewed. Ten proteins are encoded by the COVID-19 genome; one of them is the S protein, as aforementioned, because a glycoprotein exists in the virus-infected region (Fig. 6). The S protein is a significant therapeutic target, ensured its location, and targetable using antibodies

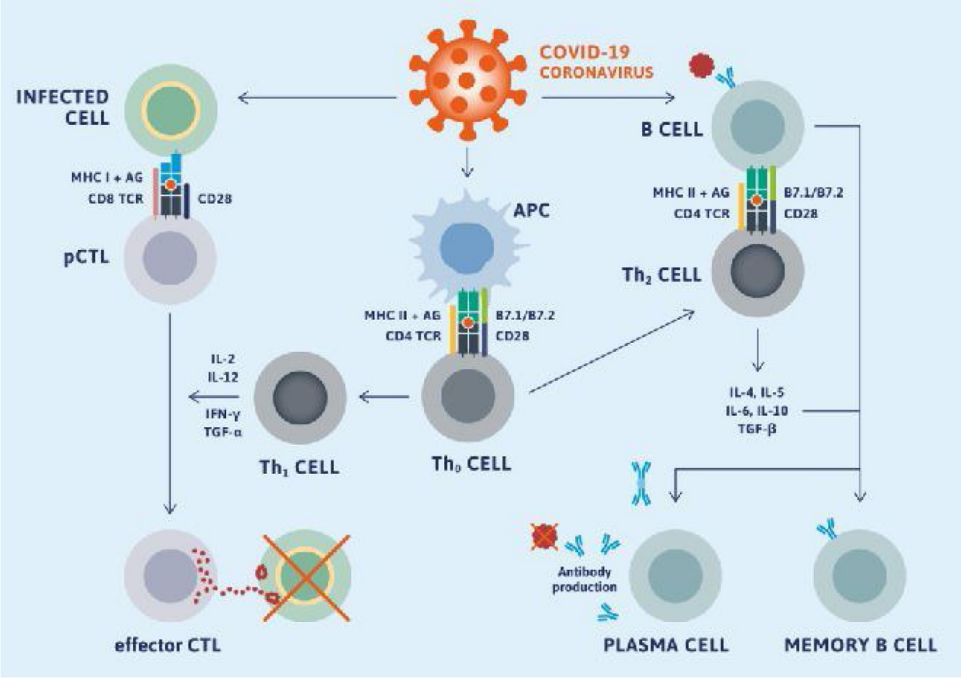

Fig. 6. Adaptive immune response against coronavirus requires stimulation of B cell and T cell epitopes [95].

Table 4
Reference peptides.

Allele	#	Sequence	Reference
A*0101	309	VTEHDTLLY	[96]
A*0201	42	VLDFAPPGA	
A*0301	52	AVAHKVHLMYK	[97]
A*1101	315	AVFDRKSDAK	[98]
A*2402	288	AYAQKIFKIL	[99]
B*4001	417	REDQWCGSL	[100]
C*0102	369	QYDPVAALF	[101]
C*0401	369	QYDPVAALF	[102]
C*0701	211	YLHARLREL	
C*0702	70	NYFNRMFHF	
DRB1*0401	139	AKFVAAWTLKAAA	[103]

Table 5
Number of epitopes with a minimum 60% stability [95].

	min 60% hits	Enrichment factor
A*0101	14	2.1
A*0201	15	6.1
A*0301	41	1.8
A*1101	49	1.4
A*2402	30	1.5
B*4001	30	1.6
C*0102	3	31
C*0401	1	ND
C*0701	3	5.3
C*0702	3	16
DRB1*0401	22	4.2

[93]. The formation of neutralizing antibodies' immunization of animals with S protein-oriented vaccines is very effective in preventing infection by homologous coronavirus [94]. If human cells are infected by virus entities, epitopes from any of that viruses' proteins can theoretically be bound and presented by MHC-1 receptors on host cell surfaces, leading to the stimulation of CD4 and CD8 T cells to provoke antibody-mediated and cell-mediated immune responses.

Case study-1

At the University of Copenhagen, researchers net MHC made in-silicon predictions of epitopes presented by 11 MHC-1 alleles that covered approx. 90% of the Asian population. Using that approach, they compiled a list of 100 candidate epitopes for the following MHC alleles—A*0101, A*0201, A*0301, A*11:01, A*2402, B*40:01, C*0401, C*0701, C*0702, and DRB1*0401—resulting in 1100 MHC/peptide binding studies. For the project, they partnered with Intavis and Intavis, who synthesized the COVID-19 epitopes assessed in the study. Using their unique neoscreen technology, they performed in vitro binding studies of the epitopes. The study identified 159 epitopes that stably bind the MHC-1 allele and 22 that bind the tested MHC-II alleles [95]. The relevant data are listed in Tables 4 and 5.

Case study-2 [105]

As of March 13, 2020, outside China, there were 32 countries with more than 100 COVID-19 cases [104]. The highest number of infections was found in seven countries: the United States (n = 2294), France (n = 3671), Germany (n = 3675), Spain (n = 5232), South Korea (n = 8086), Iran (n = 11,364), and Italy (n = 17,660). The number of confirmed cases in the other 25 countries was fewer than 1200 [105]. The related data is presented in Table 3.

The change of R_0 and R_t is connected to the proportion of individuals who have immunity in their body to that pathogen in that population. The alternative method of estimating R_t for a pathogen including the population is by multiplying R_0 through the proportion of the population of individuals considered non-immune to that pathogen. In this perception, R_0 will only have a similar level of R_t if there are no immune persons in the population. It indicates that any partial pre-existing immunity to the infecting elements is able to decrease the number of expected secondary cases emerging.

Whenever this perception is applied in case of herd immunity to control the COVID-19 epidemic, the fatality rate of the coronavirus is between 0.25% and 3.0% of the estimated population (ie, the measured number of people who may die from affecting this virus), but when the population attains the P_{crit} herd immunity level, it can be difficult to accept (Table 6).

Case study-3

Dong et al. [106] experimented on patients by using various methods. Initially, they used sera, but no significant result was observed. Subsequently, the team focused on NP and S-RBD. To determine optical dilutions, the serum from a patient and human

Table 6
Estimates of SARS-CoV-2 effective reproduction number (Rt) of 32 study countries (as of March 13, 2020), and the minimum proportion (P_{crit}, as % of population) necessary to have recovered from COVID-19 with subsequent immunity, to halt the epidemic in that population. [105].

Study countries	Population infected by COVID-19	Estimates of effective reproduction number (R_t) (95% CI), (n = 32)	Minimum proportion (%) of total population required to recover from COVID-19 to confer immunity (P_{crit})
R_t >4			
Bahrain	210	6.64 (5.20, 8.61)	85.0
Slovenia	141	6.38 (4.91, 8.38)	84.3
Qatar	320	5.38 (4.59, 6.34)	81.4
Spain	5232	5.17 (4.98, 5.37)	80.7
Denmark	804	5.08 (4.60, 5.62)	80.3
Finland	155	4.52 (3.72, 5.56)	77.9
R_t (2–4)			
Austria	504	3.97 (3.56, 4.42)	74.8
Norway	996	3.74 (3.47, 4.04)	73.3
Portugal	112	3.68 (2.86, 4.75)	72.8
Czech Republic	141	3.57 (2.88, 4.45)	72.0
Sweden	814	3.44 (3.20, 3.71)	70.9
United States	2294	3.29 (3.15, 3.43)	69.6
Germany	3675	3.29 (3.18, 3.40)	69.6
Switzerland	1139	3.26 (3.05, 4.78)	69.3
Brazil	151	3.26 (2.99, 3.55)	69.3
Netherlands	804	3.25 (3.02, 3.51)	69.2
Greece	190	3.12 (2.67, 3.67)	67.9
France	3661	3.09 (2.99, 3.19)	67.6
Israel	143	3.02 (2.56, 3.59)	66.9
United Kingdom	798	2.90 (2.72, 3.10)	65.5
Italy	17,660	2.44 (2.41, 2.47)	59.0
Canada	198	2.30 (2.07, 2.57)	56.5
Iceland	134	2.28 (1.90, 2.75)	56.1
Rt (1–2)			
Iran	11,364	2.00 (1.96, 2.03)	50.0
Australia	199	1.86 (1.71, 2.03)	46.2
Belgium	559	1.75 (1.55, 1.97)	42.9
Malaysia	197	1.74 (1.61, 1.88)	42.5
Iraq	101	1.67 (1.41,1.97)	40.1
Japan	734	1.49 (1.44, 1.54)	32.9
Korea	8086	1.43 (1.42, 1.45)	30.1
Singapore	200	1.13 (1.06, 1.19)	11.5
Kuwait	100	1.06 (0.89, 1.26)	5.66

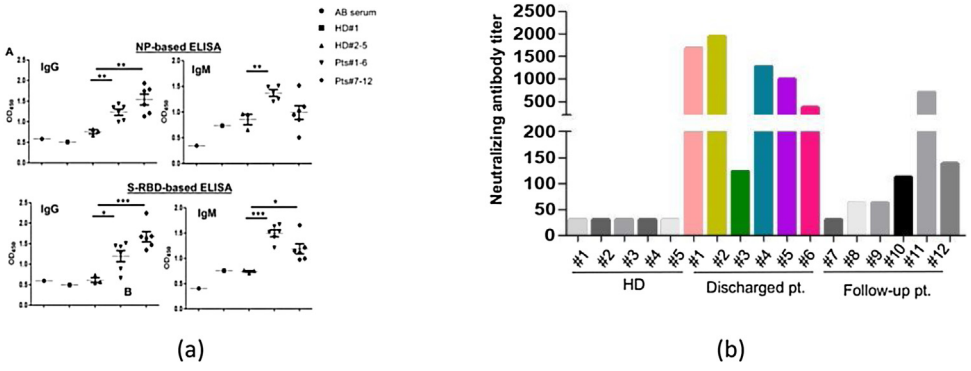

Fig. 7. Detection of antibody responses to recombinant SARS-CoV-2 proteins in patients with COVID-19. (A) Serological responses of 12 patients with COVID-19 to recombinant NP (top) and S-RBD (bottom). The experiment was performed in duplicate. (B) Measurement of neutralizing antibody titers by pseudovirus-based assay. The experiment was performed in triplicate. NP, nucleocapsid protein. S-RBD receptor binding domain of spike protein. HD, healthy donor. Pt, patient. HD#1, serum was collected in 2018. HD#2–4, the sera were from close contact. *P < **P [106].

AB serum was titrated. For IgM a dilution of 1:50 and for IgG a dilution of 1:150 were used. Compared with healthy donor groups, NP- and S-RBD-specific IgM and IgG antibodies were both detected in the area of newly discharged patients (Fig. 7). Compared with those of healthy donors, Anti-SARS-CoV-2 IgG antibodies were also more clearly observed than IgM in the followed-up patients. These findings indicate that patients with COVID-19 mounted IgG and IgM responses to SARS-CoV-2 proteins, especially NP and S-RBD, and suggest that patients who are infected could maintain their IgG levels, at least for 2 weeks. Because the RBD domain of the S protein has been shown to bind to the human receptor ACE2, the existence of antibodies against it may suggest the neutralization of SARS-CoV-2 infection. To assess that phenomenon, they performed a pseudovirus particle-based neutralization assay. Patients #1, 2, 4, and 5, all within the discharged group, had high levels of neutralizing antibody titers. Those findings demonstrate that most

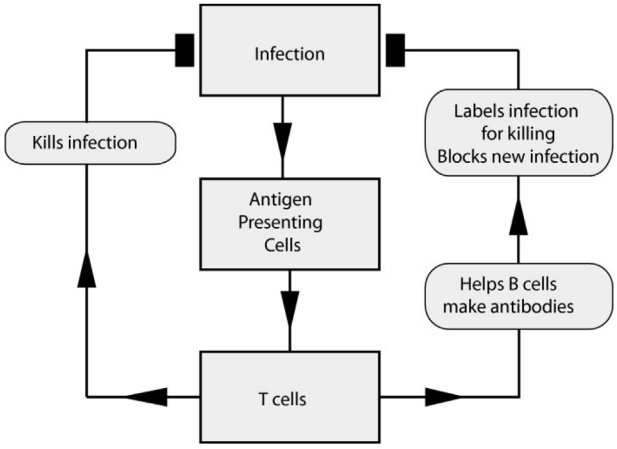

Fig. 8. The adaptive immune response to infection [111].

recently discharged patients had protective humoral immunity to SARS-CoV-2. Except for patient #11, the followed-up patients had lower levels of neutralizing antibody titers than the recently discharged other patients, and all were positive except for patient #7, who was negative.

Potential challenges in immune system development

An effective immune system must have the ability to interpret changes in the world around it and respond properly; however, it must overcome challenges to work in different environments with different pathogens (Fig. 8). Most of the time, the immune system encounters something new and considers it harmless, but in some cases, that response can be dangerous. An efficient immune system must have the ability to distinguish this. It should have the ability to adapt to strange environmental changes to fight against infections. A healthy immune system has symbiotic microbial farms and reacts to a harmful infection. When pathogens enter the body, they attempt to use it as a host, and the immune system poses many threats. A different door is used for every infection to enter a cell, and blocking these routes of entry can stop an infection before it begins. The immune system neutralizes an infection by producing antibodies; however, this must be conducted at the proper time. An immune system—ideally—must stop an infection before it has established a foothold in the body [107–111].

Suggested food, vaccination, drugs, and supplementary for the immune system for COVID-19

According to the World Health Organization, healthy foods and hydration are vital. Individuals consuming a well-balanced diet are healthier with a strong immune system and have a reduced risk of chronic illness, infectious diseases. Vitamins and minerals are vital. Vitamin B, insoluble in water, protects from infection. Vitamin C protects from flu-like symptoms [112]. Insufficient vitamin D and vitamin E can lead to coronavirus infection [113]. Vitamin D can be found in sunlight, and vitamin E can be found in, for example, oil, seeds, and fruits. Insufficient iron and excess iron can lead to risk [114,115]. Zinc is necessary for maintaining the immune system [116]. Food rich in protein should be the top priority because it has immune properties (immunoglobulin production) and potential antiviral activity [117–119]. Therefore, in a regular meal, individuals should eat fruit, vegetables, legumes, nuts, whole grains, and foods from animal sources (Fig. 9). Food from plants containing vitamin A should be consumed, and 8–10 cups of water should be drunk daily. Malnutrition is dangerous for patients with COVID-19 and thus proper nutrition should be provided [120,121]. Fruit juice, tea, and coffee can also be consumed. Too much caffeine, sweetened fruit juices, fruit juice concentrates, syrups, fizzy drinks, and still drinks must be avoided. Unsaturated fats, white meats, and fish should be consumed. Saturated fat, red meat, more than 5 g salt per day, and industry processed food should be avoided [122]. Along with diet, physical activity is another factor. Individuals should be active and perform physical exercise regularly to boost the immune system and should have proper sleep [123]. Although there is no registered medicine for COVID-19 treatment, hydroxychloroquine and remdesivir are prescribed and are partially effective [124].

Conclusions

This review on boosting the immune system is a potential resource for the treatment of patients with COVID-19. The process and mechanism of the immune system can be a good source of knowledge for immune system development. Further research could focus on the most recent observations regarding COVID-19 treatment. If the potential challenges can be overcome, this would be a substantial achievement. Finally, nutrition (eg, dietary recommendations) to boost the immune system should be explored and recommended because no registered medicine is available for COVID-19 treatment.

Fig. 9. Nutrition advice for adults during the COVID-19 outbreak [122].

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