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Immunological Facets of SARS-CoV-2 Infection: Host Immune Responses and Immunopathogenesis

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Abstract

The recently identified Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), responsible for the worldwide outbreak of coronavirus disease 2019 (COVID-19), has posed an unparalleled challenge to public health systems globally. Acute respiratory distress syndrome (ARDS), multiorgan failure, and asymptomatic infection exemplify illness severity, with host immune responses significantly influencing clinical outcomes. This work meticulously investigates the immunological mechanisms underlying SARS-CoV-2 infection, focusing on host–virus interactions, innate and adaptive immune responses, and immune dysregulation associated with severe disease. Important topics covered include the significance of type I interferon signaling, stimulation of dendritic cells, macrophages, and T lymphocytes, and viral entry pathways mediated by spike protein interactions with ACE2 and TMPRSS2. The review focuses on the immunopathological hallmarks of COVID-19, including antibody-dependent enhancement, cytokine storm, increased neutrophil activation, and lymphopenia. Additionally, methods used by SARS-CoV-2 to avoid host immune surveillance, such as interferon pathway disruption and antigen presentation disruption, are thoroughly examined. Additionally, a summary of vaccination programs, therapeutic drugs, and immunological therapies targeted at regulating immune responses and slowing the progression of disease is provided. This review highlights possible targets for therapeutic and preventive measures and offers a comprehensive explanation of the immunological foundation of COVID-19 pathogenesis by combining the available data. Such knowledge is crucial for enhancing the treatment of illnesses and directing upcoming investigations into new coronavirus infection

Keywords: COVID-19, Cytokine storm, Innate and adaptive immune responses, SARS-CoV-2.

Introduction

Throughout human history, numerous viral-mediated pandemics have occurred, including the Spanish flu in 1918 and the H1N1 influenza virus in 2009 and the COVID-19 pandemic (1). The host's immune system is crucial for defence against SARS-CoV-2 infection. This virus compromises the immune systems of vulnerable individuals, leading to a cytokine storm, particularly in the pulmonary region. Pneumonia cases were first recorded in Wuhan, Hubei Province, China on December 31, 2019. On 7th January 2020, Chinese health authorities determined that the causative agents of this pneumonia were a novel coronavirus, designated as SARS-CoV-2, and the sickness was dubbed COVID-19. On March 11, 2020, the World Health Organization (WHO) declared the uncontrolled global spread of the new coronavirus, SARS-CoV-2, a pandemic (2).

Individuals afflicted with COVID-19 may be asymptomatic or exhibit mild symptoms, including fever, myalgia, fatigue, severe dry cough, nasal congestion, cephalalgia, anosmia or ageusia, and pharyngitis, among others. Alternatively, they may present with severe symptoms such as dyspnoea or shortness of breath, which can culminate in respiratory failure (the predominant cause of mortality), chest pain, anorexia, and elevated body temperature. Individuals aged 60 and older, together with those afflicted by medical conditions such as diabetes, hypertension, cardiovascular and pulmonary disorders, cancer, and obesity, are vulnerable to COVID-19 infection (2, 3).

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Research on the susceptibility to COVID-19 infection in males and females indicated that the viral load in plasma is higher in males than females. Woman may possess superior immunological protection against COVID-19 due to the presence of genes on the X chromosome that are crucial for the immune system, indicating that sexual dimorphism significantly influences susceptibility to the virus (4).

The disruption of the blood-air barrier in the alveolar sacs has been identified as a significant pathophysiological alteration caused by COVID-19, leading to Acute Respiratory Distress Syndrome (ARDS). ARDS induces plasma infiltration into the alveoli, resulting in a sudden escalation of immune responses that draw monocytes and neutrophils (inflammatory cells) to the lungs. The overwhelming infiltration of inflammatory cells into the lungs compromises the organ (5, 6). In addition to ARDS, COVID-19 infections induce pathological diseases such as secondary haemop-hagocytic lymphohistio-cytosis and hyper-inflammatory syndrome with hypercytokinaemia, resulting in multiple organ failure accompanied by hyperferritinaemia (7). Dysfunction of immune system is the characteristics of COVID-19 infection (5).

Immune Responses by Interaction of Host and COVID-19 Virus

Coronaviruses are enclosed, single-stranded RNA viruses that induce illnesses in humans and avians. The strains exhibiting low pathogenicity are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU. These strains induce mild to moderate common cold symptoms in humans by infecting the upper respiratory tract, representing 15-30% of all common cold instances. Nonetheless, the highly pathogenic strains, such as those responsible for severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and COVID-19 (novel SARS-CoV-2), induce severe pneumonia by infecting the lower respiratory tract (1, 8).

The Coronavirus structure contains Spike (S) protein, Membrane (M) protein, Envelope (E) glycoproteins, Haemagglutinin esterase (HE), a shorter spike-like surface protein, and Nucleocapsid (N) protein (7) (Figure 1). The viral envelope contains structural proteins, together with membrane, envelope, and Spike (S) proteins (6). Nucleocapsid (N) and Spike (S) proteins elicit cytopathic effects by facilitating viral entrance into host cells and engaging in the replication, transcription, and assembly of the viral genome (1, 9, 10).

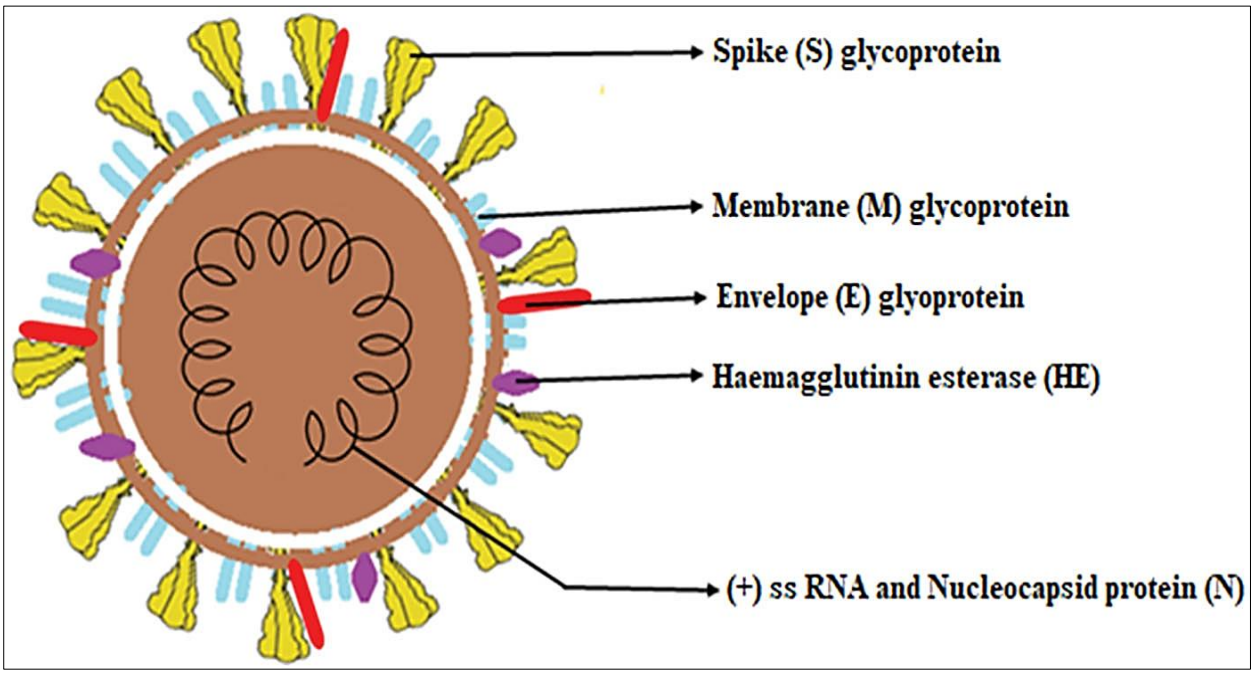

Figure 1: Arrangements of Proteins in SARS-CoV-2 (6) - Adapted with Permission

The mechanism of viral entrance into host cells involves the binding of the virus to receptors, assisted by the surface units of the S protein, which are activated by cellular proteases, resulting in the fusing of the host and viral cell membranes. SARS-CoV-2 exhibits significant similarities to SARS-CoV. They utilise the Angiotensin-converting enzyme 2 (ACE-2) receptor and the TMPRSS2 serine protease, which facilitate the priming of the S protein (6, 11-15). A membrane protein is present in nearly all organs, with significant expression levels in type 2 alveolar cells (10, 16). The virus disseminates efficiently among humans via the S protein of SARS-CoV-2, which exhibits a strong affinity for ACE-2 receptors. (17, 18).

SARS-CoV-2 stimulates both innate and adaptive immune responses in the human body. The immune system attempts to manage the infection by suppressing viral multiplication and inflammation, resulting in the eradication of infected cells from the body (19, 20). Dendritic cells (DC) and mast cells (MC) in the lungs are the primary initiators of the immune response to viral invasion in the alveolar epithelial cells. The pathogenic virus is often internalised by dendritic cells (DC), which present the viral antigen as an antigen-presenting MHC complex to circulating naïve T cells, resulting in T cell activation. (21-23). Activated effector T cells subsequently travel to the site of infection, producing numerous cytokines against the invading virus, including interferons (IFN), tumour necrosis factors (TNF), cytotoxic molecules (perforin and granzyme), and chemokines. (24). The pathogen is ultimately eradicated by the reduction of viral genome replication and the substantial recruitment of T cells to the infection site, leading to enhanced innate and adaptive immune responses (25-27).

COVID-19 and its Clinical Manifestations

The COVID-19 pandemic has exerted a global influence in a brief timeframe owing to the virus's rapid transmission rate and significant shedding capability (28). Immunocompetent individuals and young children are either asymptomatic or exhibit modest clinical symptoms. Nonetheless, immunocompromised individuals and the elderly exhibit severe symptoms that may result in mortality. This lethal infectious virus has several types of pathogenesis due to age disparities among patients (29).

Liu and his team have observed significant alterations in serum leucocytes in all COVID-19 infected patients, which persist throughout the duration of the infection. A minor reduction in total leukocyte counts in slightly infected patients may result from temporary lymphocyte depletion (30). In the initial phase of infection, elevated leukocyte and neutrophil counts were noted, particularly in severely infected patients, as a response to pro-inflammatory cytokines (31). These pro-inflammatory cytokines stimulate innate immune responses. Cytokine signalling cascades (IL-6, IL-1β) are activated and facilitate the clearance of viruses by neutrophils. NETosis, an oxidative pathogenic mechanism, is typically utilised by neutrophils to eliminate viruses, during which substantial quantities of oxidative enzymes, including MPO, NADPH oxidase, and nitric oxide synthase, are released into the extracellular environment. If malfunctioning, it may result in widespread inflammation and microvascular thrombosis, leading to pulmonary damage. (29, 32). A retrospective analysis indicated that 83.2% of individuals infected with COVID-19 during the acute phase demonstrated lymphopenia at least once (33). Lymphopenia is a significant pathological characteristic associated with disease severity in COVID-19 patients (29).

Innate and Adaptive Immune Responses

T cells responses against the viral infection are well documented; however, less information is available for coronavirus infection. An increased level of infiltration of inflammatory cells in the lung tissues is a prominent pathological finding in severely infected COVID-19 patients, as confirmed by the bronchoalveolar fluid (BALF) of patients during the course of infection (34). However, researchers reported that most people suffering from SARS CoV infection had a hyperactive immunological response, accompanied by unrestricted activation of macrophages, increase in neutrophil count with the decrease in the number of T cells and lymphocytes (6, 35-37). Briefly, the innate and adaptive immune responses to SARS- CoV infections can be grouped into three categories.

a) Role of CD8+ T Cells

The response of Immune system against any viral infection depends on communication of antigen and antigen presentation cells (APC) on viral entry into the body. The cells infected with the virus are recognized by the cytotoxic T lymphocytes (CTLs) as the viral peptides are presented by Major Histocompatibility Complex I (MHC I), thereby, producing a signal for activation of CD8+ T cells that results in apoptosis of the infected cells. Numerous reports on the connection between different polymorphisms of MHC and SARS- CoV susceptibility are found but very little information about this relationship in COVID –19 are reported. Understanding MHC polymorphism and COVID19 susceptibility can be useful to develop medications to prevent COVID –19 infections (1).

The variants of T lymphocytes such as Helper T cells (CD4+), Cytotoxic T Cells (CD8+) and Regulatory T cells are significantly reduced in seriously affected persons than less serious patients in which the regulatory T cells play an important role to maintain an equilibrium state of immune response by hindering the process of stimulation, division and function of pro- inflammation of CD4+cells, CD8+ cells, B cells and Natural Killer Cells (38, 39). CD4+ and CD8+ cells initiate the primary immune response against the invading pathogen (virus in this case) and aid in the clearance of the virus (CD4+ by cytokine derivationand CD8+ cells by cytotoxic responses). However, the quickness of the viral clearance depends on the quantity of these cells (6, 40-43). Despite the fact that the human body had all these inbuilt capabilities, the novel SARS- CoV –2 shows different unexplained ways to abscond the immune responses of the host, one of which is inducing the apoptosis of T cells. The severe phase of COVID 19 manifested reduced number of T cells accompanied with an abrupt decrease in the number of CD4+and CD8+ T cells (6, 44, 45).

b) Role of Macrophages and Dendritic Cells

The interaction between the invading virus with macrophages and dendritic cells are responsible for establishing the early innate and the following adaptive immune responses to the virus in the host by recognizing the attack through pathogen associated molecular patterns (PAMPs). In CoV case, the RNA in the viral genome are PAMPs acknowledged by the endosomal RNA receptors like TLR3, TR7, TR8 and TLR7 (1, 46). These TLRs, on immediate identification by the invading pathogens, undergo activation in the respiratory tract, thereby producing different kinds of inflammatory cytokines, chemokines and various chemical mediators in the lungs. Some chemokines such as CCL5 have the potential to attract CD8+ T cells for elimination of the attacking pathogens while TLR3 on macrophages activated by the virus produce antiviral interferons as aprotection mechanism. Such overexpression of chemokines and interferonscause severe inflammation (6, 47).

c) Type I Interferon System

It is an innate immune response against viral infections which can inhibit replication of viral genome in the early phase. Type I IFN directly interferes with the ability of viral replication at the early stage of infection (1).

These alterations in the host due to viral attack altogether leads to changes in the normal immune responses and uncontrolled release of inflammatory cytokines in the lungs contributing to cytokine storm and finally damage of the organ (Figure 2) (7, 48).

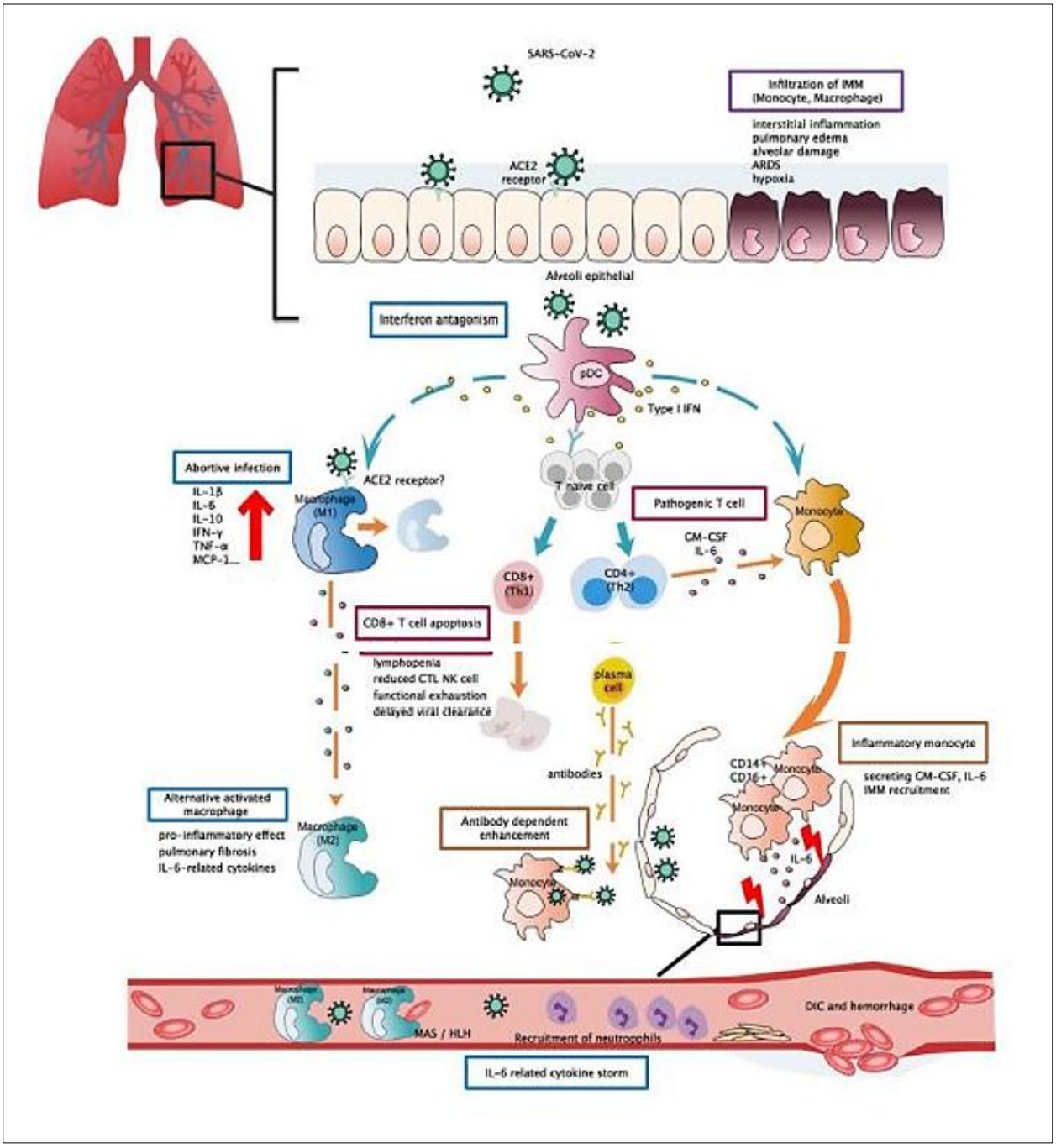

Figure 2: Potential Immunopathogenesis in COVID-19 Infections (7) - Adapted with Permission

Strategies to Escape Host Innate Immune Response by the SARS-CoV-2

SARS- CoV- 2 uses the same strategies to escape the innate immune reponses of the host like those used by SARS- CoV and MERS- CoV. Some important strategies are listed below (1):

a) The process of recognition as well as Type I IFN signalling is inhibited.
b) MHC class I and Class II molecules present in macrophages or dendritic cells are down regulated.
c) Such downregulation results in the impairment of antigen presentation, finally leading to impairment of the activation of T cells.
d) The downstream signalling cascade related to the pattern recognition receptors can be acted upon by various proteins encode by SARS-CoV-2, hence checking the efficiency of the receptors.

Humoral Immune Responses

When the patients get exposed to SARS-CoV- 2, the body responds to the viral entry by production specific IgM antibodies in a few days. It is followed by generation of the IgG antibodies specific to the virus in a week (49, 50). In SARS- CoV infected persons, the levels of IgM antibody against the virus in the serum decrease while that of IgG antibody retain for many years. The most immunogenic antigens are the Nucleocapsid (N) and Spike (S) proteins. The antibodies against N protein emerge first and can be considered as the initial and authentic serum marker for the exposure to the virus while the S protein antibodies exhibit little lately, leading to their binding to the virus envelope (1).

Studies show that the antibodies present in the serum of a COVID-19 recovering person SARS-CoV-2 can neutralize the virus in cell cultures (9, 10). Hence, the IgG antibody against the S protein can be regarded as the serum marker for the exposure to the virus as well as the recovery indicator of the disease caused by the virus (1).

Antibody dependent enhancement (ADE) is also seen in flavivirus and other coronaviruses, according to which the entry of the virus and its infection is enhanced by the interaction of antibodies through viral protein, Fc segment of IgG and receptors of the immune cells of the host (29, 51). It is, therefore, a matter of worry and concern in the development of vaccine and strategy of therapeutic uses based on antibody (1). However, this mechanism of enhancement is uniquely seen in cells of experimental models (52, 53).

Cytokine Storm - an Important Feature in COVID-19 Infection

There are reports indicating a very high cytokine and chemokine levels in COVID-19 infection such as IL-1, IL-1ra, IL-6, IL-8, IL- 10, IFN – Ɣ, MCP- 1, FGF2, MIP- 1A, TNF –a etc (54, 55). In severely ill patients, significant increase in the cytokines such as IL-1β, IFN- gamma, IP- 10, MCP-1, MCP-3 and IL-1ra can be observed while Th-1 cell related cytokines like IL-2, TNF- α, IL-1β, and IFN-gamma as well as Th – 2 cell related cytokines such as IL-4 and IL- 10 can also be detected accordingly (29, 56). A negative correlation exists between the changes in cytokines with the lymphocytes level and T cell-based CD molecules, which suggest a powerful role of association between the cytokine storm and adaptive immunity. At the time of recovery of mildly infected patients, the levels of lymphocyte initially retain to its normal state, fading the cytokines level and finally became undetectable. On the contrary, the increase in lymphocyte level is not found to be followed by a sufficient elevation in cytokines in severely infected COVID-19 patients (57). It may be because the viral clearance is accelerated by the cellular immune response of the host during the early stage of infection; thereby the production of cytokines is inhibited by the activation of innate immunity leading to alleviate severity of disease (29).

Levels of following cytokines and chemokines show various changes during different stages of SARS -CoV-2 infection (29).

a) Early or acute phase
   Chemokines - IP-10, MCP-1, MIP- 1α, GSCF
   Cytokines - IL-4, IL-10, IL-2, IFN-gamma, TNF- α - attenuation of overactive innate immunity by T cells as well as negative correlation of cytokines' levels and kinetic changes of T cell counts (30).

- IL-2, IL-7, IL-10, TNF-a, IFN- gamma, IL-1β – elevated levels in ICU patients (56).

b) Crisis or terminal phase
   Chemokines - IP-10, MCP-3
   Cytokines – IL – 1ra –independent detection of the progress of the infection by IP- 10, MCP- 3 and IL- 1ra with a lethal outcome (58).

c) Phase of Recovery
   Cytokines- IL-4, TNF-α, IL-6, IL-10, IFN- gamma - impairment of recognition mediated by CD8+ CTL and immunity evasion (55).

Immunological Intervention

Several strategies are employed to treat COVID-19 infections such as

a) Use of Monoclonal and polyclonal antibodies to target COVID-19
b) Antimicrobial agents
c) Immunotherapy with antibodies specific to the virus in convalescent plasma
d) Interferons as immunomodulators like Interferon-a, Interferon-b, Interferon-c and Interferon-k
e) Interleukins as immunomodulators like interleukin 12 and interleukin 15
f) Cytokine blockers
g) Vaccines

The potential therapeutic agents for COVID-19 infections are given in Table 1.

Table 1: Potential Therapeutic Agents for COVID-19 Infection (Adopted Table) (1)

Therapeutic agents	Area of action	Mechanisms of action	References
Serine protease **TMPRSS2**	Cell	Binding of the viral spike (S) protein priming by host through ACE2	(59)
Serotonin receptor antagonist **cinanserin**	Cell	Inhibition of the 3- chymotrypsin –like (3C-like) protease	(60)
S – protein angiotensin converting enzyme-2 (ACE2) blockers	Cell	Blocking of the S protein binding to ACE 2	(61)
Antimalarial **chloroquinone**	Medical use	Inhibition of the viral envelope fusion with the membranes of endosomes /lysosomes	(62)
Protease inhibitors **Lopinavir/ ritonavir** (HIVprotease inhibitors)	Medical use	Possibly inhibition of SARS- Cov-2 protease	(63)
Antiviral **ribavirin**	Cell	Modulation of host immunity and/ or causing catastrophe RNA replication	(64)
Protease inhibitors **nelfinavir**	Cell	A selective post translational inhibitor	(65)
Nucleotide analog prodrug **remdesivir**	Cell as well as clinical use	Possible inhibitor of RNA replication	(66), (67)
Indole- derivative molecule **arbidol**	Cell	Inhibition of viral envelope fusion with cell membranes	(68)
Immunosuppressive agent **cyclosporine A**	Cell	Blockage of replication through inhibition of N- protein	(69)
Monoclonal antibody **CR3022**	Cell as well as medical use	Strong binding of the receptor binding domain of S protein	(70)
Monoclonal antibody single- chain variable region fragmnets,**scFv, 80R**	Cell	Acts against the S1 domain of S protein	(71)
Monoclonal antibody **CR3014**	cell	Neutralizing the infectivity power of the virus	(72)
Immunotherapeutic potential **covalescent plasma**	Cell as well as medical use	Neutralizing the infectivity power of the virus	(73), (74)
Interferons **IFN-a and IFN- b**	Cell	Suppression of viral replication by inducing interferons stimulated genes	(75), (76)
Cytokine blocker **cytokine IL- 37**	Cell	Inhibition of inflammation by acting on mTOR as well as increase of the function of adenosine monophosphate (AMP) kinase	(77)
Cytokine blocker **Lianhuaqingwen**	Cell	Anti- inflammatory activity, inhibition of IL-6 receptor	(78)
Cytokine blocker **Antibody against IL- 6 receptor**	Cell	Anti- inflammatory activity, inhibition of IL-6 receptor	(1)

Vaccination Approaches

COVID-19 is the major global health challenge for which scientists, experts and health authorities are putting full efforts in the development and administration of vaccines as well as enactment of preventive ways to fight off the SARS-CoV-2 virus infection (79).

Corona vaccines are given to humans to enable the immune system to get trained by the use of a harmless form of the infectious deadly corona virus, SARS-CoV-2 virus without causing any harm to the host. There are different types of vaccines for COVID-19, working differently and uniquely in introducing antigens to the human body which stimulates the immune system in triggering specific immune response and building memory so as to enable the body to fight against and prevent SARS-CoV-2 infection in the future. Different types of Corona Vaccines are listed below along with their mode of action and some examples (80) (Table 2).

Table 2: Different types of Corona Vaccines

Types of Vaccines	Mode of Action	Vaccines in Human use	Vaccines in clinical trials
Viral vector Vaccines	Use of a delivery virus or viral vector to deliver the genetic material of corona virus by which the human cells form a protein from it	University of Oxford AstraGeneca, Sputnik V	Jannsen, Cansino, Gamaleya
Genetic Vaccines	Administration of a segment of SARS-CoV- 2 viral genetic material coding a specific protein	Moderna and Pfizer/ BioNTech	Imperial College London

Inactivated Vaccines	Use of the killed virus which cause COVID-19	Covaxin	Sinovac, Sinopharm
Attenuated Vaccines	Use of weakened corona virus	-	Codagenix
Protein Vaccines	Use of proteins from the virus	-	Novavax, Sanofi/GSK

Countries all over the globe are producing different vaccines to fight off the deadly corona virus infection after passing through three different phases of tests to check their safety and effectiveness in use. Some of the vaccines are as follows (2, 80):

a) Pfizer – BioNTech COVID-19 vaccine – developed in Germany, 95% effective
b) Moderna COVID-19 vaccine – developed in Cambridge, MA, 94 % effective
c) The Sputnik - V vaccine - developed in Russia, 91.6 % effective
d) Covaxin – developed by Bharat Biotech, India, 81 % effective
e) Coronavac - developed by Sinovac in China, 67 % effective
f) The Oxford Astra Zeneca vaccine – developed in United Kingdom, 63% effective
g) Novavax vaccine – developed in US
h) Johnson & Johnson's Janssen – developed in USA

Some of the steps recommended by the CDC to reduce infection risk are (81):

a) Use of face mask in public
b) Regularly washing of hands with soap and hot water, at least 20 seconds a time
c) Use of hand sanitizer
d) Cover sneezes as well as coughing with a tissue and dispose off at a once.
e) Avoid face touching
f) Disinfection of frequently touched surfaces like doorknobs
g) Maintaining social distancing of 6 feet at least
h) Avoid crowd
i) Avoid shaking of hands
j) Stay cautious for any forms of symptoms like coughing, high fever, sore throat etc.

Conclusion

The immune system's critical role in determining disease susceptibility, development, and clinical outcome has been highlighted by the SARS-CoV-2 pandemic. This study emphasises that COVID-19 is a complicated immunopathological disorder caused by dysregulated innate and adaptive immune responses, rather than just a viral respiratory sickness. Acute respiratory distress syndrome, multi-organ failure, and severe inflammation are all caused by delayed or exaggerated immune responses, especially when it comes to excessive cytokine and chemokine production. However, early and coordinated immune activation can effectively restrict virus replication.

The immunological landscape of COVID-19 is defined by the complex interactions between host defence systems, such as poor type I interferon signalling, lymphopenia, T-cell fatigue, and hyperactivation of neutrophils and macrophages, and viral immune evasion tactics. Cytokine storm development, which connects innate immune overactivation with weakened adaptive immunity, becomes a key factor in determining the severity of the disease. Moreover, humoral immune responses highlight the need for cautious treatment and vaccine design since, while essential for viral neutralisation and recovery, they also raise questions about antibody-dependent-enhancement.

In addition to vaccine techniques, immunological therapies that target viral entrance, replication, and inflammatory cascades have been crucial in lowering disease burden and death. However, the need for individualised and stage-specific therapy approaches is highlighted by the differences in immunological responses between age groups, sexes, and concomitant diseases. Long-term immunological memory, post-infection immune dysregulation, and immune correlates of protection all require further research.

In conclusion, improving vaccine effectiveness, developing treatment methods, and strengthening readiness for upcoming coronavirus epidemics all depend on a better knowledge of the immunological mechanisms underlying SARS-CoV-2 illness. To lessen the effects of COVID-19 and other newly developing viral illnesses, clinical care and immunological insights must continue to be integrated.

Abbreviations

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Author Contributions

Khullakpam Shaheen: conceptualization, writing—original draft preparation, Debananda Singh Ningthoujam: review and initial editing, Nanaocha Sharma: final editing.

Conflict of Interest

The authors declare that there is no conflict of interest.

Declaration of Artificial Intelligence (AI) Assistance

The authors declare that they did not use AI-assisted tools (ChatGPT, OpenAI) during the writing process.

Ethics Approval

Not Applicable.

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