Immunopathogenesis and immunobiology of SARS-CoV-2

Ali A. Rabaan[1], Shamsah H. Al-Ahmed[2], Abbas Al Mutair[3,4,5], Saad Alhumaid[6], Anupam A Sule[7], Raghavendra Tirupathi[8,9], Mohamed Fawzy[10], Javed Muhammad[11], Amjad Khan[12], Abdulkarim Hasan[13,14], Dhan Bahadur Shrestha[15], Ranjit Sah[16], Manish Dhawan[17,18], Ruchi Tiwari[19], Muhammad Bilal[20], Tauseef Ahmad[21,22], Kuldeep Dhama[23]

[1]Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, Saud Arabia;
[2]Specialty Paediatric Medicine, Qatif Central Hospital, Qatif, Saudi Arabia;
[3]Research center, Almoosa Specialist Hospital, Alahsa, Saudi Arabia;
[4]College of Nursing, Princess Norah Bint Abdulrahman University, Riyadh, Saudi Arabia;
[5]School of Nursing, Wollongong University, Wollongong NSW, Australia;
[6]Administration of Pharmaceutical Care, Al-Ahsa Health Cluster, Ministry of Health, Alahsa, Saudi Arabia;
[7]Department of Informatics and Outcomes, St Joseph Mercy Oakland Pontiac MI, USA;
[8]Department of Medicine Keystone Health, Penn State University School of Medicine, Hershey, PA, USA;
[9]Department of Medicine Wellspan Chambersburg and Waynesboro Hospitals, PA, Penn State Chambersburg, PA, USA;
[10]Department of Virology, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt;
[11]Department of Microbiology, The University of Haripur, Haripur, Pakistan;
[12]Department of Public Health & Nutrition, The University of Haripur, Haripur, Pakistan;
[13]Department of Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt;
[14]Prince Mishari Bin Saud Hospital in Baljurashi, Ministry of Health, Baljurashi, Saudi Arabia;
[15]Department of Emergency Medicine and General Practice, Mangalbare Hospital, Urlabari, Morang, Nepal;
[16]Department of Microbiology, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal;
[17]Department of Microbiology, Punjab Agricultural University, Ludhiana, India;
[18]The Trafford Group of Colleges, Manchester-WA14 5PQ, United Kingdom;
[19]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Uttar Pradesh Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan (DUVASU), Mathura, India;
[20]School of Life Science and Food Engineering, Huaiyin Institute of Technology, Huaian, China;
[21]Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, China;
[22]Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing, China;
[23]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

SUMMARY

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), in a very short span of thirteen months has taken a considerable toll on humanity, resulting in over 3 million deaths with more than 150 million confirmed cases as on May 1, 2021. In the scarcity of a potential antiviral and protective vaccine, COVID-19 has posed high public health concerns, panic, and challenges to limit the spread of this pandemic virus. Only recently have a few vaccine candidates been developed, and vaccination programs have started in some countries. Multiple clinical presentations of COVID-19, animal spillover, cross-species jumping, zoonotic concerns, and emergence of virus variants have altogether created havoc during this ongoing pandemic. Several bodies of research are continuously working to elucidate the exact molecular mechanisms of the pathogenesis. To develop a prospective antiviral therapy/vaccine for SARS-CoV-2, it is quite essential to gain insight into the immunobiology and molecular virology of SARS-CoV-2. A thorough literature search was conducted up to 28th February 2021 in the PubMed and other databases for

the articles describing the immunopathology and immune response of SARS-CoV-2 infection, which were critically evaluated and used to compile this article to present an overall update. Some of the information was drawn from studies on previous MERS and SARS viruses. Innate as well as adaptive immunity responses are elicited by exposure to SARS-CoV-2. SARS-CoV-2 establishes a successful infection by escaping the host immunity as well as over activating the innate immune mechanisms that result in severe disease outcomes, including cytokine storm. This review summarizes the immunopathology and molecular immune mechanisms elicited during SARS-CoV-2 infection, and their similarities with MERS-CoV and SARS-CoV.

Keywords: SARS-CoV-2, COVID-19, innate immunity, adaptive immunity, immunopathology, immunobiology.

INTRODUCTION

As of May 1, 2021, more than 3 million people have died out of over 150 million affected, and the entire world has been affected by the newly emerged coronavirus known as severe acute respiratory syndrome 2 (SARS-CoV-2), the cause of the currently ongoing coronavirus disease 2019 (COVID-19) pandemic [1, 2]. SARS-CoV-2 was first identified in Wuhan, China, at the end of 2019, thereafter spread swiftly throughout the globe and posed massive panic, high global health concerns, lock down scenario in most of the countries, and challenges to check its spread, however still due to the second wave of SARS-CoV-2 the cases and mortality are presently continuously being seen as rising day by day [1-3]. The exponential spread of COVID-19 throughout the world has resulted in a great havoc not only in the health sector but also in the economic status of countries worldwide. SARS-CoV-2 follows human-to-human transmission through close contact, while air-borne spread has also been reported as a dominant route [4]. SARS-CoV-2 is likely to have an animal origin, spillover and cross-species jumping events, zoonotic and reverse zoonotic concerns as well as evolution and emergence of several variants of the virus have altogether led to havoc during this ongoing pandemic [5-7]. A spectrum of symptoms and multiple clinical manifestations are observed in COVID-19. The prominent COVID-19 feature is acute respiratory distress syndrome (ARDS), while neurological, gastrointestinal, cardiological manifestations along with heart failure, kidney damage, and even multiple organ failure have also been observed in severely affected COVID-19 patients [8]. Hypercoagulopathy is seen in COVID-19 patients with severe clinical symptoms [9]. The elderly population, people with comorbidities and immunocompromised status, are more vulnerable to infection, and in such patients, severe disease outcomes of COVID-19 occur [10]. Very high and continuous efforts are being directed by worldwide researchers to introduce effective drugs, therapies, and vaccines to counter COVID-19, and only recently few of the vaccines are introduced successfully, and vaccination program has been started up in some countries [11-14].

The contagious nature of COVID-19 has resulted in a large number of individuals with severe infections with high mortality risk, requiring intensive care units (ICU) for special care. On January 30, 2020, the WHO declared COVID-19 as a Worldwide Public Health Emergency [15]. Since the first COVID-19 report of, several research studies have been carried out to have a better understanding and insights into the epidemiology, clinical characteristics, associated risk factors, and mode of transmission of the pandemic virus [16, 17]. Several extensive research studies have been conducted to identify the disease etiology in detail, the genomic organization and mutation rates, the structural aspects, and its similarity with other coronaviruses (CoVs) [18-24]. These studies depicted the virus entry in the host cell via ACE2 (angiotensin converting enzyme 2) receptors employed for host cell binding [18], its intracellular proliferation, and the immune responses elicited by the host against SARS-CoV-2 [25, 26]. Although these studies have been aimed

Corresponding authors
Ali A. Rabaan
E-mail: arabaan@gmail.com; ali.rabaan@jhah.com
Kuldeep Dhama
E-mail: kdhama@rediffmail.com

at developing robust diagnostic tests, management strategies, development of effective antiviral agents, and ultimately, the production of an effective and efficient vaccine, till date there are no effective treatment regimens; however, few vaccines are now available for COVID-19 [11, 13, 27]. To develop an effective antiviral and/or vaccine for COVID-19, a thorough understanding of the immune-pathogenesis and immunobiology of SARS-CoV-2 should be elucidated. A very few studies exist that have evaluated the immune behavior of COVID-19 in the host body. Mostly, information comes from similar studies conducted on earlier SARS-CoV and MERS-CoV coronaviruses that emerged during 2002-2003 and 2012 [28]. The host innate and adaptive immune mechanisms work together to limit viral infections. The innate immunity/first line of defense includes physical, chemical, and cellular defense mechanisms while the adaptive immunity/second line of defense acts by developing immunogenic memory and by the production of neutralizing antibodies against the antigens.

Hence, this work elucidates the immune-pathogenesis and immunopathology of SARS-CoV-2 infection, the relationship of the immune responses with the clinical spectrum of COVID-19, and an insight into the role of innate and adaptive immunity.

CORONAVIRUS

Coronaviruses (CoVs) are RNA viruses with unique glycoprotein spikes (80 and 160 nM), giving the appearance of a crown like structure. The genome of the coronaviruses ranges from 27-32 kb [29], making them the largest coronaviruses on the earth [30]. They cause severe respiratory and gastro-intestinal tract infections, and pulmonary CoVs are considered from long to be a source of respiratory tract infections in domestic animals and humans [31]. The family of coronaviruses comprise of four genera viz., alpha (α), beta (β), gamma (γ), and delta (δ) [32]. The human coronaviruses (HCoVs) belong to either alpha CoVs (HCoV-229E (named after a student specimen coded 229E, using standard tissue culture) and NL63 (NetherLand 63)) or β-CoVs (SARS-CoV, MERS-CoV, HCoV-OC43 (Organ Culture 43), and HCoV-HKU1 (Hong Kong University 1)) genera as shown in Figure 1 [33].

The four HCoVs (HCoV-229E, HCoV-OC43, HCoV-HKU1 and HCoV-NL63) generally cause mild infections, such as diarrhea and common cold [34]. In contrast, the other three HCoVs (MERS-CoV, SARS-CoV, and SARS-CoV-2) cause severe lower respiratory tract infections, and due to their highly pathogenic nature, they can lead to develop extrapulmonary manifestations and ARDS [33].

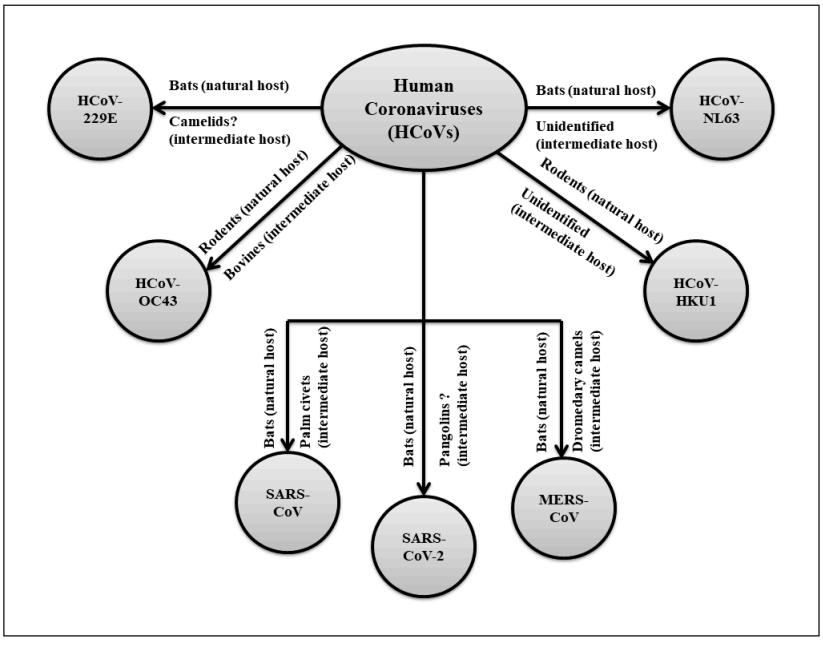

Figure 1 - Human coronaviruses and their natural and intermediate hosts.

CoVs, with high rates of mutability, are highly pathogenic and infect a vast number of hosts ranging from different animal species to humans having a spectrum of clinical symptoms. The resulting disease severity can vary from symptomless state to a severe condition requiring intensive medical care and hospitalization [2].

CoVs cause infections in various vital organs, including the gastrointestinal, respiratory, renal, heart, hepatic, and neurological systems, and worsening of respiratory disorders and bronchiolitis [34, 35]. Until the SARS outbreak in 2002-2003, CoVs were not considered very infective in humans. Until then, the two most familiar types of HCoVs were HCoV-OC43 and HCoV-229E that were thought to cause mild infections in immunocompromised individuals [36]. Due to pathogenic nature, the second coronavirus outbreak of MERS-CoV emerged in 2012, arisen in the Middle Eastern countries [37].

ANGIOTENSIN-CONVERTING ENZYME 2 - RECEPTOR FOR SARS-COV-2

The SARS-CoV-2 utilizes special host cell receptors, ACE2 to gain access into the host cell. As a transmembrane metallocarboxypeptidase, ACE2 consist of a C-terminal collectrin-like domain (CLD) and the N-terminal peptidase domain (PD). The N terminal of the ACE2 receptor, is vital for the fusion with the virus S protein (Figure 2) [38]. Furthermore, the viral S protein cleaved into the S1, and S2 subunits, then the S1 subunit binds with the N-terminal of the
ACE2 receptor. [38] The S2 subunit allows the viral fusion with the cell membrane, which is considered an essential phase for virus invasion [38-40] (Figure 2).

Angiotensin-converting enzyme displays a pivotal role in the renal and cardiac functions and blood pressure by converting angiotensin I into angiotensin II which is a crucial modulator of cardiac and renal functions and maintenance of blood pressure [41]. ACE is expressed extensively in most of the human organs, like heart, testis and kidney. The ACE2 gene encodes for ACE that proficiently catalyzes the cleavage of C-terminal residue of numerous peptides that are not related to the renin–angiotensin system [42, 43]. Though several studies have reported the ACE2 expression in various tissues, intestinal epithelium presented the highest expression levels of ACE2 mRNA. Due to the association of SARS-CoV with acute lung injury, the pulmonary expression and function of ACE2 in the pulmonary system have been extensively studied [44, 45]. In the pulmonary system, ACE2 is mostly expressed in the goblet and mucociliary cells within nasal epithelial and bronchial cells [45]. Recent studies have reported that upon pharmacological inhibition of the TMPRSS2, required for S protein priming by the SARS-CoV-2,

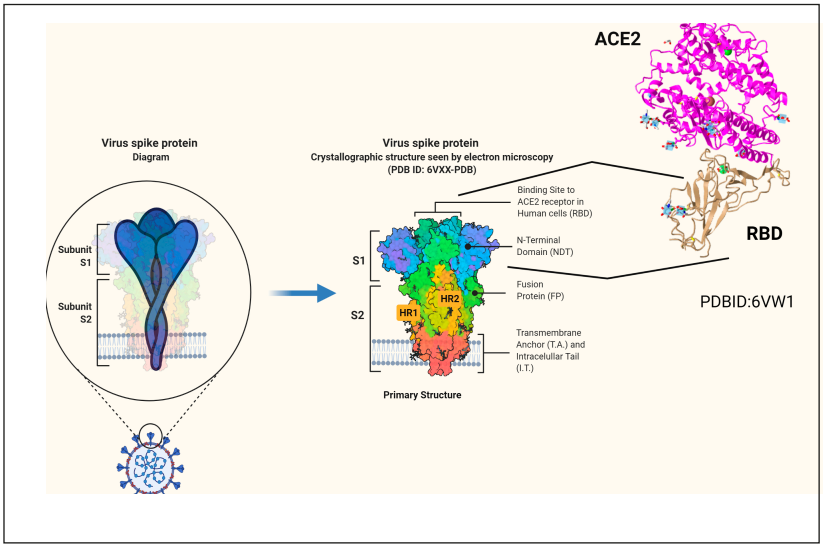

Figure 2 - A molecular interaction between the receptor binding domain (RBD) of the S-protein and ACE2 receptor. The S1 subunit of the S protein binds with the ACE2 and initiates the fusion of viral particle with cell membrane. The figure was created with BioRender.com and the molecular structure of ACE2 was obtained from NCBI protein database.

and the SARS-CoV-2 entry into the host cells via ACE2 could be inhibited [46].
The virus attachment process is followed by the cleavage of ACE2 by ADAM17 and other sheddases from epithelial cell surfaces, and ACE2 is released into the airway surface liquid [47]. ADAM17 also concerts the membrane form of the IL-6R-a to the soluble form (sIL-6Ra), which is required to trigger transcription factor STAT3 in the non-immune cells [48]. Further, the activated STAT3 then activates the proinflammatory nuclear factor kappa B (NF-kB) pathway [48]. Thus, simultaneous activation of STAT3 and NF-kB following SARS-CoV-2 infection in the respiratory epithelium leads to multiple autoimmune and inflammatory disorders [48]. Since IL-6 is considered a surrogate marker of cell senescence, its expression increases with age and hence explains for the increased age-dependent COVID-19 mortality.
Under both constitutive and stimulated conditions, the airway surface liquid contains soluble ACE2 [49]. It has been found that ACE2 can suppress viral entry into cells in a feedback, which suggests that a reduction in ACE2 shedding by ADAM17 and other sheddases might be associated with COVID-19 pathogenesis [50].
The expression of ACE2 is modulated in the lung disorders, such as acute lung injury, which is triggered by SARS infection following virus attachment to AECs. It has been reported that upon virus binding to the epithelial cells, the enzyme activity and expression of ACE2 is significantly reduced [51, 52]. In an animal model-based study, it was observed that the binding of SARS-CoV to ACE2 resulted in decreased ACE2 expression and a significant increase in acid aspiration pneumonia [53]. This can be explained in terms of the mechanism that the downregulation of ACE2 upon SARS infection increases the expression of angiotensin II, which subsequently increases permeability of vessels and thus inducing lung damage [53, 54]. The ARDS development followed by SARS-CoV infection may be due to severe lung inflammation induced dysregulated renin-angiotensin pathway [54]. ACE2 is also reported to induce lung fibrosis by modulating the infiltration of neutrophils in the lungs. This is achieved by hindering Ang II/AT1R axis that triggers pulmonary fibrosis [55].
Human ACE2 acts as the receptor for both SARS-CoV [56] and SARS-CoV-2 [57]. The attachment ability of the SARS-CoV-2 viral S protein with ACE2 receptor is relatively weaker as compared to SARS-CoV [57, 58]. Other receptors, like CD26 or DPP4 employed by MERS and SARS-CoV can also be involved in SARS-CoV-2 pathogenesis [59, 60].

COVID-19: IMMUNOPATHOLOGY

Although the mechanism of COVID-19 pathogenicity is not well described; various reports suggest that it shares a similar mechanism SARS-COV. The human-to-human mode of transmission exerts a pivotal contribution to the pathogenesis [16, 19, 57, 60]. Interestingly, the SARS-CoV and SARS-CoV-2 both utilize ACE2 as entrance receptors, while the proteases act as the entry activators [61]. The SARS-CoV-2 can also utilize the CD147 for attaching to host cells [61].
Extracellular matrix metalloproteinase inducer (TMPRSS2)/CD147 is the central protease involved in the activation of SARS-CoV-2. The single-cell genomics has shown the expression of ACE2 and TMPRSS2 on different cells [45]. This observation suggests the contribution of some other proteases (for example, cathepsin B and L) in the proteolysis and activation process.
Besides the ACE2, pattern recognition receptors (PRRs) also present an indispensable role in the virus-mediated immunopathogenesis. The PRRs help in recognizing the infecting pathogens that includes different viruses [62]. After the interaction of the viral receptors with the surface proteins, viruses initiate several host immunity responses, like activating and enhancing inflammatory factors, maturation and activation of dendritic cells and upregulation of the type I interferons to prevent virus spread [62].
The SARS-CoV-2 activated both innate and acquired immune responses of the host. Upon activation by the virus, CD4+ T cells release various cytokines and mediators that activate the B cells and the cytotoxic T cells. The triggered B cells then generate virus specific antibodies (IgG and IgM). The activated CD8+ T cells mediate the cytotoxicity and engulf the viral-infected cells. Although the presence of complement factors (C3a and C5a) and antibodies by the host immune cells are imperative in fighting the viral invasion, the SARS-CoV-2 is likely to escapes the host immune

response by overwhelming T cell functioning by the induction of apoptosis of T cells [63].

Asymptomatic COVID-19 patients or with a mild illness are not hospitalized. In several symptomatic infected individuals, the infection occurs with mild cough symptoms, fever, and body aches and then disappears in 7 to 8 days, and patients recover. Serological studies of such recovered patients have shown increased concentrations of virus-specific neutralizing antibodies and enhanced production of antibodies secreting B-cells. Further, several clinical studies have noted an increase in T cells, including CD8+ and CD4+ cells, as well as follicular helper T cells ($T_{FH)}$ in improved patients [64-66]. Nevertheless, recent evidences unveiled that an exaggerated and dysregulated immune response in severely infected COVID-19 patients with elevated proinflammatory cytokines levels is thought to start disease pathogenesis and lead to severe complications and pulmonary deterioration [67].

Several computational approaches, such as the Viral-Track tool, have been employed to decipher the viral immune response in host tissues. The Viral-Track tool has been exploited to screen the scRNA-seq data of different viruses [68]. Employing this approach, a study reported the changes in the SARS-CoV-2 infected lungs. This tool identified the presence of other human viruses, such as human metapneumovirus in the monocytes representing that SARS-CoV-2 has dampened the IFN response that has enabled the co-infection of other viruses [68].

The pathogenesis of COVID-19, therefore, can be explained to be consequence of anomalous host immune response or over activation of immunity in COVID-19 individuals. The over activation of the host immune response generates exceedingly elevated levels of chemokines, cytokines, and free radicals. This sudden rise in the local levels of the cytokines, chemokines, and free radicals (the cytokine storm) induces severe injuries in the lungs tissues and other vital organs resulting in multi-organ misfunctioning and associated death [69]. ARDS is among the known cause of death in COVID-19 [16]. Nevertheless, the specific underlying mechanism reason is unknown, and speculated to be ARDS in COVs infections [66]. Studies have shown a consistent chemokine signature in SARS-CoV-2 infection in spite of the reduction of IFN-I and -III responses [70].

INNATE AND ADAPTIVE IMMUNITY AGAINST COVID-19

Innate immunity

A very little is known concerning the innate immunity elicited by the SARS-CoV-2 in the infected patients. In an investigation including 99 COVID-19 patients, increased neutrophils (38%), low lymphocytes (35%), and high serum IL-6 (52%), and CRP (84%) were observed [19]. In another study, comparing the COVID-19 patients requiring ICU with the patients not requiring ICU, a similar pattern of high neutrophils and reduced total lymphocytes count was observed in the patients requiring ICU. The increased levels of neutrophils and decreased lymphocytes were also linked with severity and mortality [18]. COVID-19 persons undergoing ICU had elevated plasma levels of several cytokines, like MCP-1, IP-10, TNFα, and MIP-1A [16]. Similar observations of sudden rise of local pro-inflammatory cytokines were detected in MERS-CoV and SARS-CoV infections. Macrophages have been perceived as critical players in developing proinflammatory and innate immune response and are considered crucial immune cells in the immunopathogenesis of COVID-19. In severely ill patients, neutrophils were found significantly higher than the mild and low infection levels. Further, the lungs' impaired blood vessels are characterized by a higher number of lymphocytes and monocytes in COVID-19 patients. Moreover, a significantly reduced lymphocyte concentration was linked with the severity of the SARS-CoV-2 infection [71]. On the other hand, in severe infection cases, the natural killer (NK) cells number was recorded significantly lower than the macrophages [72]. The decrease in NK cells along with other immune cells of adaptive immune response, like T cells especially $CD8^+$ cells can be considered as a possible cause of the severe lung damage and poor prognosis of the disease in certain group of the people [72].

Further, several studies reported a plethora of cytokines that include IL-6, IL-1β, IL-12, IL-1, TNF-α, which are involved in generation of a hyper inflammatory response against COVID-19 [73, 120]. An unregulated release of cytokines so called cytokine storm significantly drives the fatality of. Cytokine storm is a grotesque pathologic situation determined by increased cytokines and interleukins production such as IL-6 [74]. Various

research reports have been established that COVID-19 patients with inadequate prognostic traits suffer from diverse medical implications like multiple organ breakdown and ARDS due to cytokine storm [19]. This suggests that the cytokine storm might have a significant involvement in progression and disease severity [75].

Interferon type I responses and its related cascades are mainly responsible for an effective innate immune response against viral infections. These responses elicit innate immune response by controlling viral replication.

It is believed that the host cell receptor of ACE2 is largely expressed in a small subgroup of cells *i.e.*, the type 2 alveolar cells [76]. Several studies have suggested that SARS-CoV directly infects the immune cells (*i.e.*, macrophages) and may infect T cells and mediates the SARS-CoV pathogenesis [28]. However, there are ambiguities whether SARS-CoV-2 infects the immune cells, like T-cells. Certain reports confirmed that there are only a nominal proportion of lung monocytes/macrophages that express ACE2 receptor [76]. The minimal ACE2 expression in the potential lung immune cells indicates the existence of some other SARS-CoV-2 receptors in the lung cells or other modes of entry.

To produce an effective antiviral defense, innate immune cells must identify the virus invasion efficiently by PAMPs. The endosomal RNA receptors, TLR3, TLR7 and RIG-I/MDA5, and the cytosolic RNA sensor recognize the genomic RNA and the intermediates formed in the process of replication of the genomic RNA of the coronaviruses, such as the dsRNAs. NF-κB and IRF3 gets activated and are translocated to the nucleus acting as transcription factors for downstream signaling molecules, such as the type I IFN and other pro-inflammatory cytokines [29]. This mechanism acts as the first defense line against the virus at the point of entry [29]. This is followed by activating JAK-STAT pathway by Type I IFN via IFNAR pathway, resulting in the phosphorylation of STAT1 and STAT2. The phosphorylated STAT1 and 2 then form a complex with IRF9. The STAT1/2/IRF9 complex translocates into the nucleus to induce the expression of ISGs [29]. The activation and mounting of the type I IFN immunity limits the infection at an early stage.

The coronaviruses suppress the type I IFN. These viruses interfere with the type I IFN pathway resulting in the suppression of type I IFN expression which in turn suppresses the IFNAR downstream signaling. This virus induced suppression of the type I IFN pathway is related to disease severity [69]. These viruses suppress the type I IFN mediated defense mechanism at virus recognition step and also after the induction of type I IFN pathway. At the recognition step, the SARS-CoV ubiquitinates and degrades the RNA sensor molecules (TRAF3/6 and MAVS), and thus inhibit the nuclear translocation of IRF3 [77]. MERS-CoV also suppresses the type I IFN induction utilizing these mechanisms.

Additionally, MERS-CoV utilizes the mechanism of repressive histone modification to escape the type I IFN defense mechanism [77]. After type I IFN expression, viruses are capable of suppressing/inhibiting the IFN signaling by various mechanisms such as decreasing STAT1 phosphorylation [29]. The structural (such as M, N) as well as non-structural viral proteins mediate this inflection of IFN defense mechanism. The genomic sequence similarity of SARS-CoV-2 with MERS-CoV or SARS-CoV and the presence of additional genomic sequence elements, it is believed that SARS-CoV-2 also employs similar mechanisms in modulating the type I IFN defense mechanism [57]. However, additional mechanisms may also be involved in dampening the host cell immune responses.

Elevated neutrophil and monocyte-macrophages influxes have been detected in the deadly cases of MERS-CoV or SARS-CoV [28, 78]. The dysregulation of type I IFN and inflammatory monocyte-macrophages resulted in fatal pneumonia complications [69]. Therefore, excessive type I IFN and increased infiltration of myeloid cells are the major causes of lung damage negatively affecting the infection outcome. It is believed that delayed type I IFN induction in COVs infections leads to poor control of virus entry that results in increased influxes of hyperinflammatory neutrophils and monocytes-macrophages. These disproportionate increases in the levels of the innate immune cells manifests in lung immunopathology resulting in pneumonia or ARDS. Similar mechanisms are expected in the case of SARS-COV-2. Active proliferation of SARS-CoV-2 induces the over secretion of type I IFN and increased influx of macrophages and neutrophils. The hyper activation of the neutrophils and macrophages in

turn results in the hyperproduction of cytokines. As seen in MERS-CoV-2 and SARS-CoV infections, similar alterations in total neutrophils and lymphocytes are observed in COVID-19. It can be speculated that SARS-CoV-2 triggers a tardy type I IFN response and inefficient control at an initial infection stage. The observations that the individuals with underlying co-morbidities with week immunity are highly vulnerable to COVID-19 and the infection is less severe in the young children, when the innate immunity is most active, certainly designate the key role of innate immunity [16].

Adaptive immunity

The adaptive immunity against viral infections is predominantly mediated by Th1 type immunity response. APCs-mediated antigen presentation induces the helper T cells to produce cytokines that activate the CTLs that kill the cells infected with virus. While in response to the microenvironment created by the cytokines released by the activated helper T lymphocytes and B lymphocytes are activated leading to clonal selection and antibody production against the virus (adaptive/humoral immunity). Humoral immunity, utilizing the neutralizing antibodies limits the virus infection at later infection stages and prevents future infections.

The appearance of antibodies in the serum in SARS-CoV starts as fast as day 4 of the disease and is detected in infected individuals by 14 days of onset of disease. Although IgM declines with time, IgG levels have been reported even after 2 years of SARS-CoV infection [79]. However, in MERS-CoV infection, antibodies start appearing late in the 2nd or 3rd week of disease occurrence. Such weak and delayed antibody responses are reported to be related to severe disease outcomes in both SARS and MERS [79].

Limited studies have been directed to evaluate the serology of SARS-CoV-2-associated infection. In a preliminary study, the IgM antibodies have been reported to peak at day 9 and the IgG antibodies peaked by second week [28]. However, other subsequent studies reported that IgM antibodies are generated within a few days of SARs-CoV-2 exposure and specific IgGs are produced within a week of infection [19, 80].

In one study, cross-reaction with SARS-CoV was observed in sera samples of COVID-19 patients. *In vitro* plaque assay revealed that sera collected from the COVID-19 patients neutralize SARS-CoV-2, indicating a successful rise in the humoral response [19]. Although humoral response is elicited against the SARS-CoV-2 but the antibodies titer correlation with disease severity is not well established. Among the non-structural and structural proteins, the S and N proteins have the highest immunogenicity. Since antibodies against N protein are generated first, these can be potential markers for early viral exposure while antibodies for S protein are generated afterward and bind to the virus envelope. A few reports have shown the ability of convalescent plasma in neutralizing the SARS-CoV-2 *in vitro* [19, 81]. Thus, IgG secreted against the S protein can be considered a potential marker for virus acquaintance and recovery indicator.

Besides the antibodies producing and memory B-cells, T-cells are also recognized as crucial factors in clearing viral infections and providing adaptive immunity, particularly memory T cells, which shield against further infections or reinfections. The T cells, including CD8+ and CD4+, are the fundamental T-cell subsets that are employed as markers and indicators in the prognosis of disease. Recovered patients from COVID-19 showed a surplus of multi-targeted T-cell subsets that are triggered against the virus's structural and non-structural regions. Several studies have extensively reported the response of T cells in minimizing SARS-CoV infection. A study highlighted higher responses of CD8+ T cells than the CD4+ T cells in SARS-CoV infection that might be attributed to higher antibody titers while in the fatal group of patients, higher serum Th2 cytokines were detected [82]. Epitope mapping showed that about 70% of responses were elicited against the spike, membrane, envelope, and nucleocapsid proteins. In MERS-CoV, it is reported that CD8+ T cells show a rise in the early phases and correlate with disease severity, while Th1 type helper T cells dominate at the convalescent phase [83]. It is well known that the Th1 type response may be applicable for controlling SARS-CoV-2 as well. Although the CD8+ T cell response is crucial in infection control but it must be controlled to avoid lung damage.

Recently, it has been reported that the COVID-19 in rhesus macaques (*Macaca mulatta*) resulted in intensified production of T_{FH} cells and pro-inflammatory monocytes in peripheral blood. Further-

more, it has been observed that the Th1 cellular response is prevalent among the $CD4^+$ cells in lungs, blood, and other organs [84]. Besides, the enhanced production of a specific subsets of T cells, several other clinical studies found a reduction in the T cells in SARS-CoV-2 infection, which are considered as indispensable in context of providing the adaptive immunity. Further, the reduction of T cells along with the increased inflammatory cytokines (IL-6 and IL-8) levels of have been correlated with the overwhelming consequences of the SARS-CoV-2 infection [85].

A recent investigation carried out by Ni et al. (2020) has successfully correlated the SARS-CoV-2-directed cellular and humoral immunity in blood samples obtained from COVID-19 persons. Their finding shows a strong correlation between virus-specific T cells and neutralization antibody titers. Furthermore, virus-neutralizing activities in the resurged patients have been observed. It was concluded that both T and B cells can contribute a defensive role to alleviate virus infection [86]. Wu and colleagues detected NAbs from day 10-15 after the disease onset that persist afterward. As compared to young patients the middle-age and elderly infected individuals had considerably high level of spike-binding antibodies ($P=0.0003$) and plasma NAb titers ($P<0.0001$). Furthermore, the NAb titers were negatively and positively correlated with the lymphocyte counts and CRP levels, respectively [87].

The cellular immunity against the SARS-CoV-2 virus generates a pool of T-cell subsets, specific to spike protein, membrane antigens, and nucleoprotein antigens, along with a plethora of reactive proteins, approximately 23 multi specific proteins [88]. These multispecific proteins are considered essential factors that can protect against various viral immune invasions, such as mutations and mutable antigen presentation [88]. Further, they reported multifunctionality in T cells, including CD4+ and CD8+ effector T-cells providing immunity. Patients with mild symptoms showed more significant titers of CD8+T-cells than critically ill patients. These studies suggest T-cells' critical role in adaptive immune response, especially CD8+ T cells, in protecting against COVID-19; however, T-cell response mechanisms and kinetics are yet to be explored. Further, in another study, the prominent roles of CD4+ T cells specific to the spike protein have been reported in critical patients [89]. The T cells, such as CD8+ T cells, showed unusual morphological and physiological attributes (such as reduction in IL-2, IFNs, and lesser degranulation) [72].

There is a need for more extensive research to apprehend adaptive immune response towards different viral antigens in the future. Further, the research studies focusing on the quantity and production timing of the T-cell subsets are required to understand the prognosis of disease, especially in severe infection cases [90].

ANTIBODY-DEPENDENT ENHANCEMENT (ADE) IN SARS-COV2 INFECTION

Currently, there are no clinical evidences, laboratory biomarkers or immunological assays to distinguish any viral infections from immune-augmented disease, whether by determining T cells, antibodies, or inherent host responses [91]. ADE is the phenomenon that leads to enhanced infection by the pre-existing antibodies. Developing vaccine and antibody-based therapies has become a matter of concern owing to ADE [20]. ADE is well reported in other viral infections such as dengue viral infections, SARS, MERS, respiratory syncytial virus (RSV) and measles, nevertheless, for coronaviruses, ADE has been detected in cellular experimental models [92-95]. It has been illustrated (for example in dengue infection) that the symptoms development occurs much rapidly after a secondary infection with distinct serotype [92]. The establishment of an enhanced viral replication and a more severe secondary viral infection is a direct result of ADE. This is basically carried out by non-neutralizing antibodies against the virus surface antigens that form complexes with the virus surface antigens followed by binding with IgG Fc receptors present on the target cells. This results in increased access to the target cells [92]. ADE suggests that the increased severity of viral infection is not attributable to the virulence of the virus only [96].

Earlier studies on MERS-CoV and SARS-CoV showed variation in ADE mechanism compared to dengue virus [20]. Both kinds of HCoVs (SARS-CoV and MERS-CoV) enter cells under the assistance of Fc receptor (FcR). Furthermore, the SARS-CoV interact with antibodies and FcR inducing hyperimmunity which lead to causes enhanced lung injury resulted in alterations of the

functions of macrophages [97]. Numerous reports on SARS-CoV suggested that viral spike increase the chances of virus entry into the cells expressing Fc receptor [98]. However, the induction of binding between antibodies and FcR, MERS-CoV promotes viral entry [95].

Some clinical trials have suggested the safe use of convalescent plasma therapy in SARS, MERS and COVID-19 patients [99, 100]. This becomes very important in the context of convalescent plasma therapy to investigate if ADE is enhancing the coronavirus infection. Recent studies have explained molecular mechanisms underlying ADE [95]. Binding neutralizing antibodies with the S protein induce a conformational change enabling virus entry into the FcγR-expressing cells [95]. However, there is no direct evidence of magnified coronavirus replication mediated by this phenomenon. This warrants for extensive studies to investigate if this antibody mediated entry of the virus enhances the coronavirus replication in the host cells. There may be several other host factors that may exacerbate the disease outcome. Therefore, exhaustive epidemiological and genetic studies need to be performed on COVID-19 patients to find out the role of other host factors in the secondary infections. Identification of these factors will aid in controlling the viral replication during secondary infections. ADE of viral replication may be induced by the vaccine strains of the virus. Very few reports have indicated that SARS-CoV-2 antibodies may enhance the virulence of virus via amplifying the infection and immunopathology of COVID-19 through ADE, but such hypothesis warrants further confirmation [93].

CONCLUSION AND FUTURE PROSPECTS

Although quite insufficient information is presented on the molecular immunology of SARS-CoV-2 infection, it is quite evident that innate as well as adaptive immunity executes an essential role in the COVID-19 immunopathogenesis. Nevertheless, the expression of ACE2 receptors and their interaction with viral spike protein, which allows the viral access to the host cell, play a pivotal contribution to the prognosis of the COVID-19 disease. Further, the dysregulated and elevated release of proinflammatory and inflammatory cytokines is considered as an essential and inevitable consequence of SARS-CoV-2 infection in severely infected patients. The secretion of pro-inflammatory cytokines, (IL-1, IL-6, and TNF-α) leads to a hyperinflammatory response by recruiting macrophages, T and B cells in lung alveolar cells lead to ARDS. The defect in type 1 IFN immunity has been considered as a crucial feature in the immunopathogenesis of critically ill patients. Efficient immune responses are decisive to clear the virus infections, and any dysregulations in immunity responses began to the severity of the disease. Several factors have been explored, such as notable T cells reduction compared to macrophages and neutrophils have been associated with the immune response dysregulation and cytokine storm. Further, the elevated levels of neutrophils and macrophages have been connected with the poor prognosis of the infection. The molecular pathways involved in the immune response can be targeted to develop antivirals and vaccines. Extensive clinical investigations are required to understand the detailed molecular mechanism of immune responses to SARS-CoV-2. In future, a comprehensive acquaintance of the SARS-CoV-2 pathogenesis and molecular dissection of immune response generating pathways is needed to study the treatment options.

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