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Review

Host factors: Implications in immunopathogenesis of COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is more serious in people with underlying diseases, but the cause of healthy people with progressive disease is largely unknown. Host genetic factors such as ACE2 variants, IFITM-3, HLA, TMRSS2, and furin polymorphisms appear to be one of the agents involved in the progression of the COVID-19 and outcome of the disease. This review discusses the general characteristics of SARS-CoV-2, including viral features, receptors, cell entry, clinical findings, and the main human genetic factors that may contribute to the pathogenesis of COVID-19 and get the patients' situation more complex. Further knowledge in this context may help to find a way to prevent and treat this viral pneumonia.

1. Introduction

On February 11th, 2020, the world health organization (WHO) named the novel coronavirus-induced pneumonia "coronavirus disease 2019" (COVID-19), which was rapidly reached the epidemic scale [1]. WHO declared that the outbreak was a pandemic in March 2020. This virus was also named "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the international virus classification commission. SARS-CoV-2 is not the first coronaviruses-caused outbreak. Coronavirus families were the main reason for the three epidemics so far, including the Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and Coronavirus disease (COVID-19) [2].

More people have been affected by COVID-19 worldwide, compared to SARS-CoV and MERS-CoV combined [3]. COVID-19-related mortality and morbidity are increased substantially with age and general health situations such as cardiovascular diseases, diabetes, and cancers. Although many infected individuals recover, young and healthy patients might be victims of the disease [4]. The findings raise the question of how much variation in COVID-19's severity may be clarified by genetic predisposition. Human genetic factors can lead to the extremely high contagiousness of SARS-CoV-2 and the persistent disease progression demonstrated in a minor but substantial number of infected patients; however, these mentioned factors are mainly still obscure. The introduction of new preventive and/or treatment options for COVID-19 would be significantly improved by the comprehensive detection of host genetic pathways and DNA polymorphisms (variants) that attenuate the risk of infection and serious illness, including the over-exuberant immune response to the virus, which also has negative consequences [5].

2. SARS-CoV-2

According to its phylogenetic relation, SARS-CoV-2 belongs to beta coronaviruses in addition to SARS-CoV and MERS-CoV [6,7]. The family of coronaviruses has an envelope (E), membrane (M), and spike (S) in their major structural proteins [8]. Like other coronaviruses, SARS-CoV-2 are positive sense, RNA single-stranded viruses that contain a large genome (27–32 kb) compared to other RNA viruses [9,10]. The rate of genomic homology between SARS-CoV-2 and SARS-CoV and MERS-CoV is 82% and 50%, respectively [11].

In the previous SARS-CoV outbreak, the S protein was shown to promote cellular entrance by binding to the angiotensin-converting enzyme 2 (ACE2) receptor present in the host's target cells [12]. Besides, the cellular transmembrane serine protease 2 (TMPRSS2) is necessary for the priming of the S protein and subsequent fusion of SARS-CoV with the host cell membrane [13–15]. In addition, overexpression of ACE2 raises disease incidence in transgenic mice following

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infection with SARS-CoV, suggesting this receptor's role in promoting viral entry [16]. Several experiments have shown that the S protein of SARS-CoV-2 also uses ACE2 and TMPRSS2 for cell entry [15,17], and SARS-CoV-2 S protein has 10–20 times higher affinity bind ACE2 compared to SARS-CoV S protein [18].

Sequencing data revealed that SARS viruses and the ACE2 receptor blend some important amino acids, which are highly conserved in SARS-CoV-2 [19,20]. The ACE2 receptor is the main component of human infection and host dissemination of SARS-COV-2 [21].

3. Clinical features of COVID-19

Patients diagnosed with SARS-COV-2 infection may experience a wide range of clinical symptoms. The triad of fever, dyspnea, and dry cough is the most common one that may be present in many individuals. According to the patients' immunity status, SARS-COV-2 is classified as symptomatic or asymptomatic, carrier, or infective state, from profusely symptomatic to mild prodrome. Besides, gastrointestinal complications, especially diarrhea, nausea, vomiting, and abdominal pain, are frequently observed amongst patients diagnosed with this SARS-COV-2 [22,23]. According to a recent review, ocular surface manifestations occur in approximately 11.64% of individuals suffering from COVID-19. The key features include ocular pain, discharge, erythema, and follicular conjunctivitis, which occur in 31.2%, 19.2%, 10.8%, and 7.7% of cases, respectively, which can be regarded as the predominant ocular presentations among COVID-19 patients [24].

Individuals who are infected with SARS-CoV-2 may be at risk of neurological conditions like encephalopathy, encephalomyelitis, cerebrovascular accidents, anosmia, and neuromuscular disorders [25].

Of note, patients with older age, male sex, active smokers, and related comorbidities such as diabetes, hypertension, kidney disease, chronic pulmonary disease, obesity, and cardiovascular diseases are more vulnerable to severe forms of SARS-COV-2 infection [26].

According to the severity of clinical presentations, COVID-19 is generally categorized as mild, moderate, severe, and critical [26], which is provided in detail in Table 1. Significant lymphocytopenia (mainly T cells and natural killer (NK) cells), hypoalbuminemia, and anemia are usually reported in SARS-COV-2 infected patients. On the other hand, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, lactate dehydrogenase, alanine aminotransferase, alanine aminotransferase, procalcitonin, and cardiac biomarkers level increased [27].

Table 1
Different COVID-19 stages [28].

Case Severity	Clinical Presentations
Mild	• Low-grade Fever • Cough • Malaise • Rhinorrhea • Nausea • Vomiting • Diarrhea • No radiological evidence of pneumonia • Absence of mental changes
Moderate	• Fever • Respiratory Complications (dry cough, breath shortness)
Severe	• Dyspnea • Respiratory frequency 30/minutes • blood oxygen saturation $\leq$ 93% • PaO2/FiO2 ratio 50% of the lung field within 24e48h
Critical	• Oxygen Saturations $\leq$ 88% • ARDS • Multiorgan dysfunction • Metabolic acidosis • Coagulation dysfunction

ARDS: Acute respiratory distress syndrome.

4. ACE2: angiotensin-converting enzyme 2

ACE2 is an important receptor, which is generally used for cell entry in both SARS-COV and SARS-COV-2 [7,12]. This protein is encoded on chromosome X and has a catalysis function in the conversion of angiotensin II to angiotensin (1–7). Vasodilation and extra substantial modulatory impact on the cardiovascular system are the outcomes of this referred process [29]. ACE2 has three principal functions, which are summarized in Table 2.

Regarding that type II alveolar epithelial cells highly express ACE2 [34,35], more respiratory symptoms upon COVID-19 infection are expected [36]. In addition to the lungs, ACE2 is also expressed in different organs' cells, including the bladder, kidney, heart, and intestine [35,37]. Different organ expressions of ACE2 may explain some non-respiratory complications of COVID-19, such as cardiac injury, kidney failure, and diarrhea [36,38].

As alveolar cells are infected, the S1 protein of SARS-CoV-2 and ACE2 transmembrane domains bind to decrease the amount of ACE2 [39]. Therefore, Ang II production is relatively or absolutely increased, which leads to increased cytokine production, macrophages infiltration, presence of more adhesion molecules such as monocyte chemotactic protein 1 (MCP1), IL-6, selectin E, and vascular cell adhesion molecule 1 (VCAM-1) which results in endothelial dysfunction [40,41]. Furthermore, ACE2 downregulation decreases the protective effect against lung injuries [42], which causes pulmonary edema, increased pulmonary capillary permeability, and infected individuals with the severe form of the disease may expire due to respiratory failure [39].

In the context of SARS-CoV-2 infection, it should be noted that in addition to the classic RAS/ACE formation of Ang II, Ang II creation can happen through alternative pathways by different proteases such as tryptansin, cathepsin G, tunin, kallikrin, kimase and neutral endopeptidase. These proteases can convert Ang I to Ang II [43,44]. The majority of these proteases are not sensitive to ACE suppressors and are present in certain tissues such as the myocardium, arteries, lungs, kidneys, or brain. It is noteworthy to mention that suppression of ACE with the help of these inhibitors reduces the level of Ang II for a short time so that it returns to its original state one week after treatment with ACE suppressors [45]. A study showed that the use of ACE and Ang II receptor inhibitors (ARBs) in experimental models cause to increased ACE2 expression [45]. Part of the protective function of ARBs and ACE is due

Table 2
Different functions of ACE2.

No.	The main functions of ACE2	Reference
1	ACE2 functions as a negative protein regulator in the renin-angiotensin-aldosterone system (RAAS), which plays a significant role in defense of the cardiovascular system and other tissues by acting on angiotensin II.	[30]
2	ACE2 is able to remove C-terminal remainder from other vasoactive peptides such as kinetensin, des-Arg bradykinin and neurotensin in in vitro assessment. The kinin metabolites, des-Arg^{9}-bradykinin, and desArg^{10}-kallidin activate the B1 receptor along with G protein, which augments in reaction to tissue injury and may be crucial in inflammatory responses.	[31,32]
3	ACE2 plays a major role in the absorption of amino acids in the intestine and kidneys due to its interaction with amino acid transporters.	[33]
4	ACE2 operates on peptides such as apelin-36 and apelin-13 with great catalytic performance. These apelins have recently been recognized as inner ligands for the human APJ receptor, which is a homolog of angiotensin type 1 (AT1) receptor. Studies show that while systemic administration of Aplin-13 causes hypotension in rats, Aplin-13 causes vasoconstriction in endothelium-denuded coronary arteries.	[32]
5	B-casamorphin and dinorphine A 1–13 are opioid peptides as well as ACE2 substrates. These two peptides modulate pain sensation by activating delta and kappa G protein opioid receptors and may have negative effects on contraction of cardiomyocyte.	[32]

to over-regulation of ACE2. Thus, over-regulation of ACE2 may prepare further receptors for virus entrance and augment a higher viral load with an unfavorable prognosis [46]. It also suggests that in individuals using ACE suppressors, activation of alternative pathways may play an important role in the creation of Ang II [47]. A clinical trial is currently underway to evaluate the effects of ACE/ARB inhibitors (ClinicalTrials.gov Identifier: NCT04330300) on SARS-CoV-2 infection. If alternative pathways are important in the formation of Ang II, ACE/ARB inhibitors are unlikely to be involved in the clinical courses of SARS-CoV-2 infection [48].

The expression of ACE2 receptors may be affected by the coding-region variants in ACE2. However, the variant distribution and allele frequency records were considered to contribute to ACE2's role in acute lung injury and lung function [49].

Experts claim that in infected COVID-19 patients using Renin-Angiotensin-Aldosterone System (RAAS) inhibitors, ACE2 may be considered as a therapeutic target [50]. Recent clinical studies demonstrated that human recombinant soluble ACE2 (hrsACE2) hinders coronavirus loads by a factor of 1000–5000 [51]. Regarding that, the outcome is dose-dependent; it will be different according to the virus and hrsACE2 total number. The author also confirms the knowledge obtained from normal cell cultures in engineered miniature replicas of blood vessels and kidneys [52].

It's worth noting that Asian populations have the same level of ACE2 expression as other populations [53]. However, the higher the expression of ACE2-related quantitative trait loci variants, the more different predisposition and response to SARS-CoV-2 is expected in different populations at the same time [49]. So far, no mutations or polymorphisms in ACE2 have been linked to S protein binding resistance [49]. ACE2 variations that affect the interaction between SARS-CoV-2 and the host cell were discovered after a large genomics database study in over 400 populations. Individuals with S19P, I21V, E23 K, K26R, T27A, N64 K, T92I, Q102P, and H378R polymorphisms are more susceptible to virus infection, according to Stawiski et al. [54]. Furthermore, those with other ACE2 variations, such as K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y, showed a decreased affinity to bind SARSCoV2, which could have a role in COVID-19 [54]. It's worth noting that these variants are uncommon, and more research into patient clinical outcomes is desperately needed [55].

In the Iranian population, 17 missense single nucleotide polymorphisms (SNPs) were reported so far. V485L, which is a viral glycoprotein mutation, showed a low affinity for virus binding. These variants might be considered as a natural resistant mutation among the Iranian population. On the other hand, S331F mutation increases COVID-19 infection [56].

In Europe and the East Asian population, a cohort study introduced two ACE2-related variants, including K26R and I468V, as two variants with lower affinity to bind the viruses S protein [57]. Due to S protein importance, these two identified variants may potentially change the kinetics of viral binding and internalization, which may account for prominent disease severity. An experiment by Pinto et al. on 700 lung transcriptomic databases from patients with hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) revealed that global ACE2 expression was significantly higher compared to healthy patients' lungs [58]. Therefore, this may clarify why these patients experience a more severe form of COVID-19; nevertheless, several other studies highlighted that the higher ACE2 expression has a protective role against different lung injuries [59,60]. Further experiments are necessary to assess whether ACE2 modulation is a direct consequence of the underlying comorbidities or increased/decreased ACE2 expression in some anatomical locations/tissues in these individuals is causative for extreme COVID-19 [61].

ACE2 polymorphisms and expression levels have also been theoretically linked to the increased severity of COVID-19 in males. Although some studies found that ACE2 expression in males is generally higher in comparison to females [62,63], some others reported the equivalent expression level among both genders [64,65]. These contradictory results have led some researchers to conclude that it is either the pattern or distribution of expression of ACE2 in different anatomical locations rather than global differences in intensity of expression that cause sex-based variations in the severity of disease [66,67]. Due to ACE2 is expressed on the chromosome X, males carry and express only a single ACE2 variant; however, females express a mosaic pattern of ACE2 [66]. If men possess an ACE2 variant that is more permissive for infection with SARS-CoV-2, all cells express the risk variant [61].

Altogether, AEC2 has a complex and not yet fully described function in cellular SARS-CoV-2 infection so far, which makes it attractive to study more about how SARS-CoV-2 interferes with and affects ACE2 expression and modulation and their consequences on viral replication [68].

4.1. The expression of the ACE2 on immune cells, especially tissue macrophages, and their roles in inflammatory response

SARS-CoV-2 generally attacks the human pulmonary system. A study showed that ACE2 has little or no expression on basic human alveolar epithelial cells and alveolar epithelial cells of the paraffin segment of lung tissue [69]. Remarkably, this study found that at steady-state ACE2 was highly expressed in human Kupffer cells, alveolar macrophages, and microglial cells, and increased in LPS-activated M1 macrophages. Nevertheless, at steady state, the majority of immune cells in human peripheral blood, including newly isolated $CD14^+$ monocytes, lacked ACE2. This suggests that circulating monocytes probably increase ACE2 expression after immigrate to lung tissue with differentiation into alveolar macrophages. These investigations indicate the significance of alveolar macrophages for the pathogenesis of lung injury in COVID-19 infected individuals [70]. Liao et al., demonstrated that there are many proinflammatory macrophages in the bronchoalveolar lavage fluid of patients with severe COVID-19 [71].

Through postmortem studies of COVID-19 patients' spleens and lymph nodes, Feng et al. discovered the viral nucleocapsid protein (NP) of SARS-CoV-2 in $ACE2^+CD169^+$ macrophages, but not in $CD3^+$ T cells or $B220^+$ B cells [72]. These data suggest that lung macrophages may be directly attacked by SARS-CoV-2 and play a key role in the onset and spread of COVID-19. Another study showed that alveolar macrophages exhibit the type 1 macrophages phenotype [73], while a subtype of $CD169^+$ resident lung macrophages, located mainly around the airways, adjacent to the bronchovascular bundle sympathetic nerves, have macrophage-type 2 specification and show anti-inflammatory effects [73]. Thus, these two types of macrophages have important functions in surveillance and maintaining of pulmonary system homeostasis [70].

Decreased ACE2 expression inhibits the destruction of des-Arg^9 bradykinin (DABK) by lung epithelial cells [74]. Increment DABK levels activate the DABK/Bradykinin receptor B1, which in turn secretes proinflammatory mediators through the lung epithelium. In particular, macrophage inflammatory protein2 (MIP2), C-X-C motif ligand 1 (CXCL1), C-X-C motif chemokine ligand 5 (CXCL5), and tumor necrosis factor-alpha (TNF)-α are released, leading to severe neutrophilic reactions and subsequently worsen the lung damage. In addition, overexpression of ACE2 through genetic therapy enhances the MAS pathway, increases Ang-(7-1) production, inhibits the extracellular signal-regulated kinase (ERK)/nuclear factor kappa B (NF-κB) pathway and thus Prevents severe inflammatory reactions in acute respiratory distress syndrome (ARDS) [75,76].

Also if SARS-CoV-2 reduces the expression of ACE2, Ang-(1-7) production is expected to be decreased. It can reduce MAS activation, which leads to an increase in ERK/NF-κB, as well as the release of IL-6 and TGF-β which significantly increase the fibrotic and inflammatory responses [77]. Indeed, the severity of COVID-19 has been observed to be related with increased plasma levels of cytokines such as IL-6 [78,79]. In addition, reports indicate that levels of procalcitonin, a known marker of

systemic inflammatory response syndrome, are five times higher in severe COVID-19 patients [80,81]. Therefore, measurement of IL-6 and procalcitonin is vital to assess the COVID-19 severity and improve prognosis. Therefore, inhibition of this inflammatory reactions decreases mortality in severe patients with COVID-19 [77].

5. TMPRSS2: transmembrane protease serine-type 2

The second host protein implicated in SARS-CoV-2 infection is serine Protease TMPRSS2 [61]. TMPRSS2 is a protease from the serine protease family of transmembrane type II; it causes the S protein to induce viral cell membrane fusion on the cell surface, and it also facilitates the entrance of coronaviruses into the host cell [82,83]. TMPRSS2 cleaves the S protein in the epithelial cells of SARS-CoV-2 infected patients, facilitating viral dissemination and pathogenesis by viral identification through activating S protein and neutralizing virus-cell as well as cell-cell fusion antibodies [84]. In the mice experimental model, it has been demonstrated that TMPRSS2 participates both in coronaviruses dissemination and immunopathology of the airways [85]. SARS-CoV-2 has been shown to use the cellular protease TMPRSS2 for S protein priming [86,87]. Besides, cell lines that express TMPRSS2 are highly predisposed to COVID-19 infection [88]. It has been found that TMPRSS2 Isoform 1 possesses 37 additional amino acids in its tail, which has not been detected in isoform 2. These additional amino acids might have a significant role in the activation of the S protein of SARS-CoV-2, which leads to viral progression in the infected individuals [89]. Cheng et al. has been previously reported that two TMPRSS2 related SNPs, including rs2070788 and rs383510, increase TMPRSS2 gene expression and remarkably predispose individuals to influenza infection [90]. Several probable TMPRSS2 related SNPs might regulate the host's cells against COVID-19 infection [55].

An intergenic SNP was identified by Russo et al., which was associated with increased TMPRSS2 expression and decreased MX1 interferon-inducible gene expression in lung tissue [91]. Individuals who carry this type of SNP are more susceptible to COVID-19 infection since this SNP increases the TMPRSS2 cell surface expression and decreases the patients' antiviral response simultaneously [61]. In an Italian cohort, Asselta et al. reported many TMPRSS2 related SNPs, which might be correlated with TMPRSS2 higher gene expression [64]. In particular, one of these variants was related to an androgen-responsive upstream enhancer of TMPRSS2, indicating another potential cause for augmented COVID-19 severity in men. Although the initially identified possible variant ACE2 and TMPRSS2 of COVID-19 are encouraging, trials of interactions between these genetic variants and clinical findings are missing in persons infected with SARS-CoV-2. However, the classification of known variants as beneficial or deleterious is premature before further research can be carried out to confirm their biology [61].

Several studies revealed that TMPRSS2 expression and distribution are compatible with ACE2 protein expression, and these two receptors are highly expressed in gastrointestinal, endocrine, kidney, bladder, urinary and male tissues but low in lung cells [92].

5.1. CD147

Given that the ACE2 receptor is expressed minimally in T cells, alternative routes of entry may be present. CD147 is expressed strongly in T cells, with evidence in favor of its role in SARS-CoV-2 invasion [93]. The entry of SARS-CoV-2 into the host cell can be mediated through the direct interaction of its spike protein and CD147 [94], which is a route of cell penetration for SARS-CoV-2. CD147 a highly common transmembrane glycoprotein named basigin, which is also referred to as a cluster of differentiation 147 (CD147) and extracellular matrix metalloproteinase inducer (EMMPRIN) [93]. This glycoprotein was first detected in 1992 as an antigen associated with the activation of T cells [95]. CD147, NRP1, and myeloid CLRs have been listed as potential viral entry points as alternatives to the ACE2 receptor [96].

The loss of this transmembrane protein or its inactivation with Meplazumab has been shown to avert the replication of SARS-CoV-2, while the viral infection is promoted by its overexpression. Interestingly, after inducing infection of SARS-CoV-2 in hCD147 mice, the lungs were found to have high viral loads. It appears that the CD147 transmembrane protein facilitates viral cell entry through endocytosis [94].

CD147 is involved in tumor development as well as infection with bacteria, viruses, and Plasmodium. As mentioned, the CD147 glycoprotein can also facilitate HIV-1 cell entry [97,98]. CD147 is responsible for stimulating the production of matrix metalloproteinases (MMPs) both in physiological and pathological processes like inflammation, tissue repair, and wound healing [96]. Receptors including CD147, angiotensin-converting enzyme 2 (ACE2), and TMPRSS2 fulfill key roles in the cell attachment and entry of coronaviruses. The CD147 receptor is expressed in epithelial, fibroblasts, and brain cells [96]. The fact that the N protein of SARS-CoV-1 was found to coprecipitate with CD147 supported the hypothesis that various viral components interact through different pathways with this transmembrane protein [96]. Furthermore, SARS-CoV-1 binding could be inhibited through the application of the HAb18G/CD147—antagonistic peptide (AP)—9 in HAb18G/CD147-expressing HEK293 cells [96]. In one study, the anti-CD147 antibody was shown to inhibit the replication of SARS-CoV-2 in a manner that was dose-dependent [99]. It is also worth noting the inhibition of SARS-CoV via the use of the CD147-antagonistic peptide-9 [100].

The spike protein of SARS-CoV-2 may use CD147 as an alternative point of cell entry [96]. In support of this hypothesis, the penetration of the human immunodeficiency virus (HIV) into T cells is through CD147. In one study, the interaction of the C-terminal domain of CD147 with the external subdomain of the SARS-CoV-2 spike protein was modeled [93]. Interestingly, recent studies have noted the aversion of diabetic complications related to COVID-19 through the inhibition of this transmembrane receptor [101].

5.2. Furin

The furin protease is expressed in tissues of various body systems, including the central nervous system, pulmonary system, gastrointestinal system, and reproductive system. This enzyme fulfills a notable role in SARS-CoV-2 infection [102,103]. With the help of this protease, the viral spike protein can be cleaved by TMPRSS2. At the spike protein's S1-S2 boundary, SARS-CoV-2 features a polybasic site that is cleaved by furin [102,103]. This mediates viral cell entry into host cells and may boost the tissue tropism and transmissibility of the novel coronavirus [103]. However, under in vivo conditions, this may not be necessary [103]. It has 5 SNPs (rs6226, rs753334944, rs16944971, rs73489557, rs6225) which were not found to be correlated with COVID-19 [104].

5.3. HLA: human leukocyte antigen

The HLA system is considered a crucial genetic factor that plays an important role in numerous viral disease outcomes, including SARS and human immunodeficiency virus (HIV) [105,106]. In some populations, it has been demonstrated that there might be a correlation between HLAs and SARS severity [107,108]. Although some experiments showed that some HLAs including, HLA-B*07:03, B*46:01, DRB1*03:01, DRB1*12:02, might be correlated with SARS vulnerability, other experiments did not verify the results [109].

Recently, a possible correlation amongst the genetic verities in histocompatibility complex (MHC) class I genes and the SARS-CoV-2 susceptibility and its severity of COVID-19 has been suggested [110]. Nguyen et al. [110] predicted the binding affinity of SARS-CoV-2–145 HLA class I alleles, and the top presenters of conserved peptides were found to be HLA-A*02:02, HLA-B*15:03, and HLA-C*12:03. They also found that B*15:27 alleles might correlate with COVID-19 occurrence. HLA-B*15:03 and B*15:27 belong to the category of B*15 and have ten

variations in nucleotides. The prediction of these alleles' peptide-binding groove may help to understand their correlation with COVID-19. Even though the total sample size in the current analysis was insufficient, these results would also be useful to examine the effect of polymorphisms of the HLA gene on COVID-19 vulnerability and patient outcomes [111].

HLA-B*46:01 gene has to lowest binding capacity to SARS-CoV-2 peptides, suggesting that individuals who carry this allele may be more susceptible to COVID-19 infection due to lower capacity for viral antigen presentation to the immune cells [110]. Meanwhile, this allele was previously reported as a risk factor for SARS-CoV infection [107]. In the Asian population, this allele is significantly associated with SARS disease severity [107].

Although HLA-A*24 did not consider a risk factor for SARS infection [112], some studies have reported the association of HLA-A*24:02 with diabetes [113,114], one of the major risk factors for COVID-19 infection [115].

Italian researchers found that the most frequent HLA haplotypes in their population are HLAA*:01:01g-B*08:01g-C*07:01g-DRB1*03:01g and HLA-A*02.01g-B*18.01g-C*07.01g-DRB1*11.04g are considered as a risk factor and protective role in COVID-19 infection, respectively [116].

Spinetti et al. showed that monocytic HLA-DR (mHLA-DR) expression was higher in non-critically ill COVID-19 patients rather than patients who are in critical situations. This reduction expression is continued even until five days after intensive care unit (ICU) admission. In this population of critically ill patients, immunomodulation interventions should be directed by an immune screening program to assess who might benefit most from a given immunological intervention [117].

HLA-DR expression was blocked by SARS-CoV-2 patient plasma, and this was partly restored by the IL-6 blocker Tocilizumab. The patient under tocilizumab therapy was followed with a rise in circulating lymphocytes. The unusual pattern of immune dysregulation in extreme COVID-19 is thus characterized by low HLA-DR expression regulated by IL-6 and lymphopenia, combined with prolonged development of cytokines and hyper-inflammation [118].

In addition, HLA-C*07:29, C*08:01G, B*15:27, B*40:06, DRB1*04:06, and DPB1*36:01 alleles frequency was higher in patients diagnosed with COVID-19; however, frequency of DRB1*12:02 and DPB1*04:01 alleles was lower in COVID-19 patients compared to healthy controls. These data might show that several HLA alleles may be correlated with COVID-19 occurrence [111].

HLA-C*07:29 was detected in one COVID-19 patient in the Chinese population, but this allele was not found in healthy controls. Hence, further investigations upon this allele are recommended in an experiment with a larger sample size [111].

5.4. MBL: mannose-binding lectin

The complement system is significantly involved during SARS-CoV-2 infection. Gao et al. showed that serum concentrations of complement proteins were higher in patients with severe COVID-19 than in patients with mild COVID-19 and healthy controls [119]. Another study based on functional gene enrichment analyzes in patients with COVID-19 reported an enhancement in genes associated with complement induction and the classical pathway [120].

Several studies have shown that compounds rich in D-mannose or L-fucose strongly glycosylate the SARS-CoV-2 S protein [121,122]. It appears that the virus interacts with lectins such as CL-11 or FCN-1 to activate the complement pathway. It reveals that the virus, by interacting with lectins such as FCN-1 or CL-11, is expressed in the alveolar epithelium [87,88] and [123]. These factors induce activation of the complement pathway in the bloodstream. Following the virus's entry into the bloodstream, conditions are provided for them to interact with complement pathway compounds such as MBL, ficolins, and CL-11 [124].

MBL is one of the serum proteins of the complement pathway. This pattern-recognition receptor, in combination with MBL-associated serine protease 2 (MASP-2), activates the complement lectin pathway via interacting with sugars on the surface of various pathogens. It has been reported that the interaction of the SARS-CoV-2 nucleocapsid protein with MASP2 results in spontaneous activation of MASP2 and C4 cleavage [119] as shown in Fig. 1. A study of 569 patients with SARS showed that MBL gene polymorphisms were implicated in susceptibility to the virus, suggesting that the complement lectin pathway is the first line of defense against the SARS-CoV [125,126]. In addition, in a study by Magro et al., deposition of complement lectin pathway ingredients such as MBL and MASP-2 and other complement proteins such as C3, C4a, C4d, and C5b-9 in the microvasculature of lung tissue samples have been shown in COVID-19 patients [127]. However, Yuan and colleagues achieved controversial results. They did not observe a significant difference in MBL genotypes between individuals with SARS and the healthy control group [128].

Accordingly, although the complement system is unnecessary for virus clearance, it has a crucial role in the immunopathogenesis of SARS-CoV-2 infection. Clinical studies need to evaluate the presence of complement proteins, MBL, and MASP-2 in the serum of COVID-19 patients. If a strong association between high concentrations of complement proteins such as MBL and MASP2 in the serum of patients with COVID-19 and an increase in disease severity is confirmed, complement targeting can be effective in reducing the pathogenesis of the disease [129].

It has been shown that the use of monoclonal antibodies such as Narsoplimab (OMS721; Omeros Corporation, Seattle, WA), which targets MASP2, could inhibit lectin-induced inflammation and endothelial cell injury [130].

5.5. IFITM3: interferon-induced transmembrane protein 3

The main target tissue of respiratory viruses such as SARS-COV-2 is the lung. Given that reported receptors such as ACE2 and TMPRSS2 have little expression in lung cells, it is hypothesized that other factors are involved in the process of virus entry into the cell and causing viral infection [92]. Huang et al. Showed that Interferon-induced transmembrane protein 3 (IFITM3) could inhibit SARS-CoV proliferation and invasion [131]. IFITM3 is a protein found in lysosomes and endosomes with a molecular weight of 15 kDa [132]. IFITMs 1, 2, and 3, as members of innate immunity, by regulating the binding of viruses and endocytic vesicles and directing them to lysosomes, respond to viral infections [133]. To prevent the release of the virus into the cytoplasm and control virus spread, IFITM3 can inhibit virus binding to the host cell by further modifying the cell membrane inflection [134,135].

The results indicate that IFITM3 is widely expressed in all organs, especially lung, liver, and female tissues, gallbladder, bone marrow, muscle tissues, and lymphoid and blood cells at the transcriptional level. The results of expression at the protein level of this molecule are quite different. At the protein level, IFITM3 is more expressed in organs such as the gastrointestinal tract, endocrine glands, bladder, kidneys, skin, and male tissues, and the expression at the protein level is higher than RNA. However, in tissues such as the lung, liver, gallbladder, and blood cells, the results are different, and the expression of this molecule at the protein level in these organs is lower than the expression level of RNA. The data indicate high expression of IFITM3 in granulocytes and monocytes, while it is rarely expressed in lymphocytes (B-, T- and NK-cells). Thus, it can be stated that the expression and distribution of IFITM3 are not similar to other viral receptors such as TMPRSS2 and ACE2 [92].

IFITM3 is fundamentally expressed by resident leukocytes and epithelial cells in the airways of the lungs, which can lead to resistance to viral infection. It has been reported that viruses are more prone to cells that express less IFITM3 [136]. This molecule enhances the persistence of mucosal immune cells by increasing the assemblage of

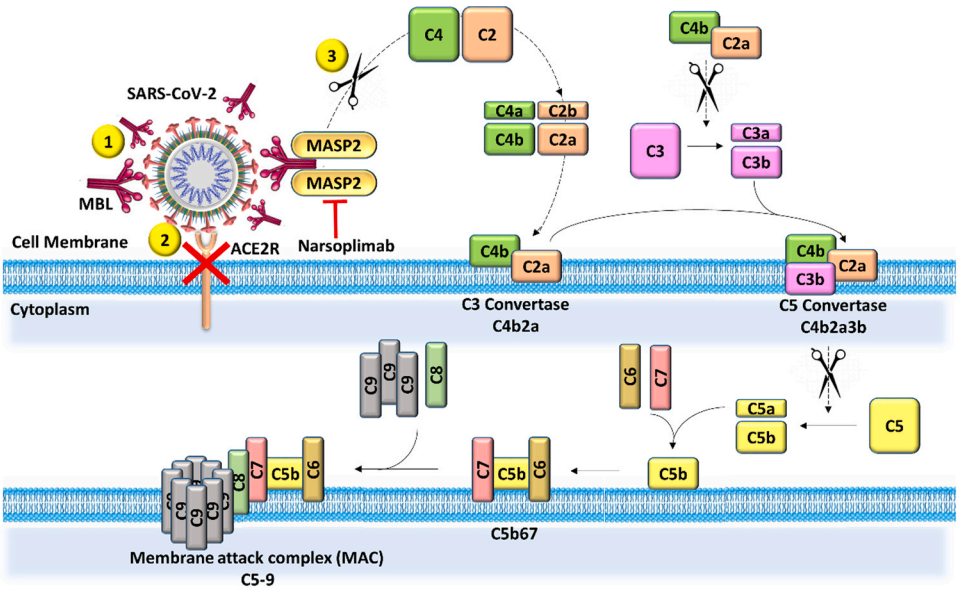

Fig. 1. The role of lectin pathway of the complement system in COVID-19 pathogenesis. 1) Binding of MBL to the glycosylated site of SARS-CoV-2 S protein by compounds rich in D-mannose or L-fucose 2) Inhibit S protein binding to the ACE2 receptor and prevent infection 3) Cleavage of proteins in the lectin pathway and the formation of membrane attack complexes (MAC). MAC induces endothelial inflammation and tissues damage. Monoclonal antibodies such as Narsoplimab, which targets MASP2, can inhibit lectin-induced inflammation and endothelial cell injury.

CD8 T lymphocytes in the airways [137]. Due to the fact that circulatory and lung immune cells express less IFITM3 Compared to other organs, it can be considered as a reason for the severity of COVID-19 and induce the cytokine release syndrome [92].

In a study, an experimental design was suggested to better comprehend the association between COVID-19 and IFITM3 for the inheritance mechanism hypothesis. In this study, Zhang et al. reported that homozygosity for the C allele of rs12252 in the IFITM3 gene was related to the severity of COVID-19 disease in an age-dependent fashion [138]. Different IFITMs (IFITMs1–3) are induced by Interferon types I and II. Numerous studies have shown that IFITMs strongly prevent viral infections caused by a wide range of enveloped and nonenveloped viruses [139]. IFITM3 rs12252-C polymorphism for severe COVID-19 may be population-related. Also, there are other polymorphisms such as rs34481144-A for the IFITM3 gene, which, unlike rs12252-C, has not been reported to affect the severity of COVID-19 in humans. In addition, the endosomal employment of IFITM3 instead, an overall increase in IFITM3 abundance causes a virus-induced phenotype. In general, IFITM3 affects the infection by various methods, including changes in the protein and fat composition of intracellular acid chambers, altered cell membrane attributes, and inhibition of hemagglutinin-mediated membrane binding, and increased cholesterol concentrations in lysosomes and delayed endosomes. Altogether, the mechanisms of inhibition of SARS-CoV-2 with the assistance of IFITM3 need further study [140].

5.6. GRP78: glucose-regulated protein 78

The Glucose Regulating Protein 78 (GRP78), also called Binding immunoglobulin protein (BiP), is an important chaperone protein involved in the folding of unfolded or badly folded proteins [141]. Normally, this protein, which is located in the lumen of the Endoplasmic Reticulum, binds to enzymes involved in the death or cell differentiation, inactivating them. These enzymes include Transcription Factor 6 (ATF6), Protein kinase RNA-like Endoplasmic Reticulum Kinase (PERK), and Inositol-requiring Enzyme 1 (IRE1) [142], which are activated by separation from GRP78. After activation of these enzymes, inhibition of protein synthesis and increased refolding occurs [142,143]. Cellular stress is one of the factors that increase the expression of GRP78 chaperones that may lead to the escaping of this protein from the ER and moving towards the plasma membrane. Subsequently, the probability of detecting the virus with SBD of the GRP78 molecule that has been transferred to the membrane increases, thus opening a way for the virus to enter the host cell [142]. Pep42 is a cyclic peptide that has been reported to bind the GRP78 overexpressed and expressed at the surface of cancer cells [144].

A study by Chu et al. showed that viruses such as bat coronavirus HKU9 (bCoV-HKU9) and Middle East respiratory syndrome coronavirus (MERS-CoV) bind to host cells through GRP78 [145]. In another study, GRP78 stimulation was observed in SARS-CoV-infected cells [146]. Although few studies have been performed on the expression of GRP78, its polymorphisms, and the function of this molecule in determining resistance or susceptibility to the coronavirus, this molecule may likely contribute to the exacerbated infection and death. Based on the available evidence, GRP78 may be used in the production of antiviral drugs against COVID-19. In addition, GRP78 antagonists may be effective in the management of COVID-19 [55].

It has been suggested that the binding of GRP78 present on the surface of human cells to the protein S of SARS-CoV-2 is a desirable procedure for the management of COVID-19 [147,148]. Palmeira et al. showed that GRP78 mRNA levels in the blood of pneumonia patients with SARS-CoV-2-positive were almost four times higher than those of pneumonia patients with SARS-CoV-2-negative [148]. Besides, another study showed that serum levels of GRP78 protein were higher in patients with SARS-CoV-2 than in patients with pneumonia or control groups [149].

GRP78 is a member of the heat shock protein 70 (HSP-70) family. With the destruction of the endothelial barrier in the lung tissue, for example, during Acute Respiratory Syndrome Distress (ARDS), the production of heat shock proteins happens, which leads to an enhancement in their amount in the blood [150,151]. Actually, intense traumas result in the release of HSP-70 proteins into the bloodstream. In a study, Haider et al. Reported that patients with ARDS had higher concentrations of the HSP-70 protein [152]. Therefore, it is assumed that the high levels of GRP78 observed in the blood of patients with SARS-CoV-2 are derived from their lung tissue, which requires further testing to confirm this [148].

To date, several inhibitors have been identified to prevent viral S protein binding to GRP78 on the surface of host cells, which play an important role in stopping or preventing disease. Imatinib, FK-614, Selonsertib, Zilucoplan, Obinepitide, and Corticorelin ovine triflutate are some of the most promising drugs. However, these results were based on work in silico, and confirmation of the antiviral effects of these drugs against SARS-CoV-2 requires in vitro investigation [148].

5.7. TLR: Toll-like receptors

Toll-like receptors (TLRs) are one of the pattern-recognizing receptors that may be contributed to the primary failure of viral elimination and subsequent progression of the lethal clinical symptoms of COVID-19, particularly ARDS with fatal respiratory failure [153]. In humans, TLRs1–10 has been observed in various cell types, especially innate immune cells such as macrophages, fibroblasts, and epithelial cells. Pathogen-associated molecular patterns (PAMPs) in microorganisms induce the activity of TLRs. These receptors play a prominent role in initiating innate immune responses through their actions, such as the production of inflammatory cytokines, IFN I, and other mediators [153], as shown in Fig. 2. Viral Single-stranded and double-stranded RNAs are detected by TLR7 and TLR3, respectively. Therefore, given that the SARS-CoV-2 genome is a single-stranded RNA, TLR7 is probably involved in the clearance of the virus [154]. Prevention of the onset of severe COVID-19 in patients with clinical manifestations can be effective by the existing agonists against TLR7, which is synergistic with common and active antiviral therapy [155].

Imai Y et al. showed that genetic inactivation of the TLR4 gene in ARDS mouse models induced by diverse noxae like SARS-CoV was related to a decline in acute lung damage, whereas TLR3 or TLR9 genes are not like this [156]. Macrophages in the lungs of patients with severe COVID-19 may be significantly involved in the secretion of inflammatory cytokines such as IL-1β, IL-6, TNF-α, and other mediators (IL-10 and IL-12) by activating the TLRs pathway [157]. Although direct activation of the TLR4 pathway by SARS-CoV-2 is unlikely, bacteria can activate this receptor [153]. One hypothesis based on acute lung damage in a mouse model suggested that TLR4 activation may be induced by phospholipid oxidation, resulting in ARDS [156]. Levels of neutrophilic myeloperoxidase have been reported to be elevated in people with COVID-19, especially in patients receiving supportive ventilation [158]. This enzyme can increase the oxidation of phospholipids [159] in the alveolar surfactant [160]. Therefore, TLR4 antagonists may be used as a drug for the treatment of COVID-19 [155].

TLR5 is another receptor that stimulates innate immune responses expressed in various immune cells such as dendritic cells, monocytes, and so on [161]. In addition, in humans, this receptor is expressed in respiratory epithelial cells and pneumonocytes [162]. Accordingly, TLR5 can enable innate protective immunity versus respiratory infection by activating primary signaling. Therefore, given that one of the common clinical manifestations related to COVID-19 is a respiratory infection, it is possible to develop innate protective immunity versus respiratory infections through the initial signaling generated by TLR5 [163].

Because bacterial flagellin is a TLR5 ligand, initial activation of this receptor by binding to flagellin may increase immunogenicity to enhance immunotherapy. Reports indicate that this process is effective in several vaccine models [164]. Flagellin also augments immunity versus viruses. Studies show that even Salmonella flagellins are promising nomination adjuvants to the influenza virus, and experiments on a mouse model have shown that treatment with flagellin could reduce the burden of influenza A virus in the lungs [165]. So far, various vaccines against viruses have been developed using TLR5 targeting. Numerous examples are noted in this direction. West Nile virus vaccine was developed using TLR5 [166]. The lentiviral vaccine was developed using cytomegalovirus and TLR5 [167].

Given that the SARS-CoV-2 genome is RNA and that some TLRs are involved in identifying the genome of microorganisms, questions may be asked about the functional roles of TLRs 3, 7, 8, and 9. However, the immunopathological results appear to be due to the interaction stage of the virus with the host, ie the interaction between the SARS-CoV-2 S protein and the human immune cells available in the alveoli [168]. Therefore, after investigating the interaction between surface TLRs in human cells and SARS-CoV-2 S protein, it was found that TLR4 has a strong binding affinity for S protein after TLR6 and TLR1. Hence, one of the reasons for developing clinical symptoms in patients with COVID-19 may be the interaction of S protein with TLR4. This interaction could provide a new way to produce drugs or TLR4 antagonists to treat SARS-CoV-2 [169]. Bhattacharya et al. showed that the S protein of COVID-19, which interacts with TLR5, is a candidate for producing the vaccine [170]. Because the vaccine is a peptide and has a shorter length than the original protein and helical structure, it has more interaction with TLRs than that of the complete protein structure [169].

At present, due to the limited therapeutic agents against COVID-19, the use of TLRs as a target for pharmacological factors may be effective in the recovery of patients with COVID-19. However, the chances of eradicating the disease are slim for decades to come [155].

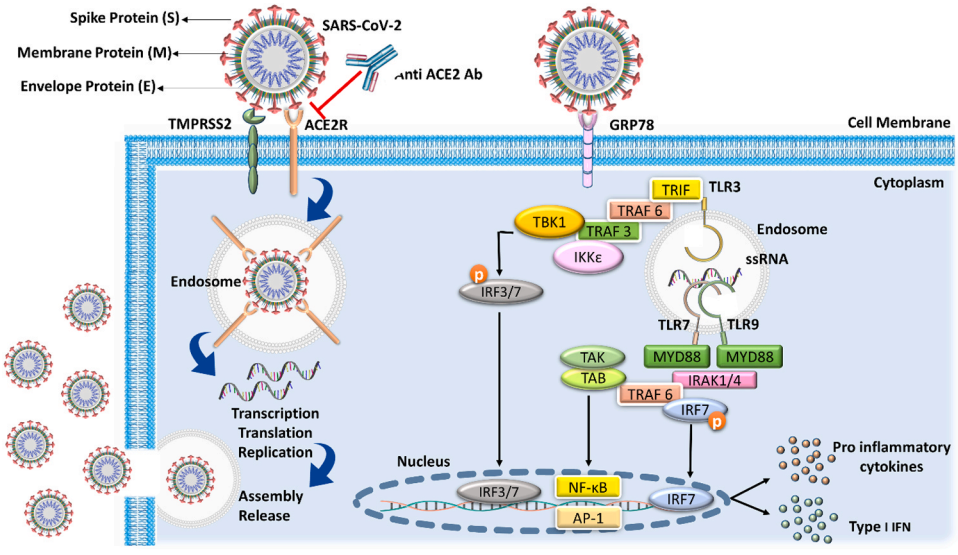

Fig. 2. Function of some host cellular receptors against SARS-COV-2. ACE2 is an important receptor, which is generally used for cell entry in both SARS-COV and SARS-COV-2. Antibodies against ACE2 receptor prevent the interaction between virus and host cell. SARS-CoV-2 has been shown to use the cellular protease TMPRSS2 for S protein priming. TMPRSS2 is a member of the peptidase S1 family, which cleaves and subsequently activates the SARS-COV-2 S protein. This membrane protein facilitates the binding of the virus to the host cell through two independent mechanisms: 1) Proteolytic degradation of ACE2, which induces virus uptake. 2) Cleavage of viral S protein, that activates the protein for cathepsin L-independent host cell entry. GRP78 is an important chaperone protein involved in the folding of unfolded or badly folded proteins. Binding of GRP78 present on the surface of human cells to the SARS-CoV-2 S protein is a desirable object for the inhibition of COVID-19. Viral Single-stranded and double-stranded RNAs are detected by TLR7 and TLR3, respectively. Given that the SARS-CoV-2 genome is a single-stranded RNA, TLR7 is probably involved in clearance the virus. Activation of the TLR pathway triggers the production of inflammatory cytokines and antiviral mediators such as type I IFN.

5.8. ABO

The ABO blood group system is made up of A and B antigens and their antibodies. The gene encoding these antigens contains alleles, including A, B, and O, which results in four genetic phenotypes A, B, AB and O [171,172]. The different expression of blood group antigens can manipulate the host susceptibility to various infections. Blood group antigens can act as receptors for microorganisms in wide ranges of infections [173].

One study found that ABO blood groups showed varying degrees of risk for SARS-CoV-2 infection. Blood group A has been shown to be associated with an increased risk, while the blood group O has been correlated with reduced risk for the disease [174]. Patrice's study demonstrated that antibodies against human A antigen may inhibit the binding between SARS-CoV and its receptor. This could be a reason why people with blood type O are less likely to get the virus [175]. However, there may be other mechanisms that need further study to be clarified.

Of note, the impacts of blood group on COVID-19 outcomes are remained elusive. Proteomic analysis of ABO locus revealed that variants in the ABO locus were correlated with CD209/DC-SIGN (Dendritic cell-specific intercellular adhesion molecule-3–Grabbing Non-integrin) levels [176]. Another hypothesis is that ABO blood group affects activity of glycosyltransferase and the venous thromboembolism risk, which is common in severe COVID-19 and have serious consequences [177,178].

The study conducted by Hoiland et al., evaluated the impact of ABO blood group on clinical indicators of critically ill patients. According to the data of this study, the distribution of ABO blood groups in the sample of patients admitted to the ICU was not different from the distribution of provincial and national ABO blood groups, whereas, more patients with blood groups A or AB compared to blood groups O or B were required CRRT (continuous renal replacement therapy) and mechanical ventilation. In addition, markers of liver and kidney dysfunction were reported to be higher in blood group A or AB, although the serum levels of inflammatory cytokines did not show any differences [179].

5.9. Apolipoproteins

In the human body, one of the lipoproteins associated with lipid metabolism as well as cardiovascular and neurological diseases such as Alzheimer's disease is APO E [180,181]. In general population, APO E gene has three different alleles with various frequencies including, E2, E3 and E4 (5–10%, 65–70% and 15–20%, respectively) [182]. The combination of these different alleles creates several genotypes such as E2/E2, E3/E3, E4/E4, E2/E3, E2/E4 and E3/E4 [182]. Various studies have conducted so far to express the potential relation between APO E polymorphism and the incidence and severity of COVID-19 [183].

It has been found that APO E increases the incidence of SARS-CoV-2 and its associated infections. SARS-CoV-2 entry sites are dependent on cholesterol, and the furin priming of this virus is also sensitive to cholesterol, and therefore, low cholesterol level protect the development of severe COVID-19 [184]. It has been hypothesized that the severity of COVID-19 can be predictable by the APO E4 genotype [185–187]. Kuo et al. (2020a) observed that people with a homozygous genotype for APO E4 were more prone to develop severe COVID-19 [188]. APO E has been shown to modulates proinflammatory pathways in a genotype-dependent manner during COVID-19 interaction [189].

It is reported that two of the apolipoproteins 1 variants are G1 and G2, were related to an increased risk of non-diabetic kidney complications in African Americans [190]. G1 variant codes for two amino acid substitutions S342G and I384M (rs73885319 and rs60910145) that nearly always occur together, while G2 variant (rs71785313) is a six-base pair deletion that results in the lack of 389Y and 388N amino acids. Several studies have mentioned that three patients were diagnosed with acute kidney injury following COVID-19 infection [191, 192]. These cases are homozygous for APOL1 G1 and the expression of chemokines was increased [193]. Thus, collapsing glomerulopathy in patients with COVID-19 was related with hazardous APOL1 variants [193].

5.10. CXCR6

CXCR6 (C-X-C chemokine receptor type 6) had high colocalization probabilities in the lung, whole blood, and T follicular helper cells, according to the colocalization analysis. At the single-cell level, DEG (Differentially expressed gene) analysis discovered that CXCR6 gene expression was lower in COVID-19 severe patients than in moderate patients in both T cells and T_{RM} cells, confirming the protective effect found in TWAS (transcriptome-wide association studies) analysis in lung and whole blood. T_{RM} cells from severe patients had a 2.24-fold decrease in $CD8^{+}$ T cell proportion and significantly higher pro-inflammatory activity than T_{RM} cells from moderate patients [194].

Previous research has found that $CXCR6^{-/-}$ significantly reduces airway lung T_{RM} cells due to altered $CXCR6^{-/-}$ cell trafficking within the mouse lung [195], which can illustrate a much lower T_{RM} cells proportion in severe patients with COVID-19 than moderate patients. T_{RM} cells in the lungs serve as the first line of defense against infection and help to coordinate the subsequent adaptive response [194,196].

A recent study showed that loss of CXCR6 reduces SARS-CoV-2 infection in lung epithelial-like cells [197]. In addition, another study reported that CXCR6 is excess for the uptake of T lymphocytes into the lungs and airways. The CXCR6-deficient mice can increase host tuberculosis and influenza control with other alternative receptors (CXCR3, CCR5, and CCR4) to activate the inflammatory response, this suggests that other activated pathways may compensate for CXCR6 deficiency in patients with severe COVID-19 [194,198].

One study hypothesized that host genetic variants lead to lower CXCR6 expression, which may reduce the proportion of T_{RM} cells resident in the lung via the CXCR6/CXCL16 axis [195,199] which disrupts the first line of defense. In addition, lower expression of CXCR6 may be associated with the "unstable" residence of T lymphocytes in the lung. Because T_{RM} plays an important role in regulating the immune system, their absence leads to violent signs of COVID-19, such as cytokine storm, Acute Respiratory Distress Syndrome (ARDS), and Major Multiple Organ Injury [200]. Finally, CXCR6 deficiency may also lead to a compensatory inflammatory response [198].

5.11. Manipulation of these host genetic factors as novel therapeutic targets

5.11.1. Decoy biomolecules

As previously mentioned SARS-COV-2 attacks host cells, especially alveolar epithelial cells, by binding to the ACE2 receptor. The SARS-CoV-2 spike protein creates a strong interaction with the ACE2 receptor [201,202], which this interaction increases the entry and replication of the virus [202,203]. It is hypothesized that targeting this connection and employment the soluble form of ACE2 could be an influential treatment [42]. Studies have shown that injection of ACE2 can competitively neutralize the virus and ameliorate lung damage [21]. It has recently been indicated that ACE2 recombinant human solution (hrsACE2) can prevent SARS-CoV-2 from entering host cells and reduce load of the virus in a dose-dependent method. These data showed that hrsACE2 is useful in the early stages of the disease. The hrsACE2 prevents viral infection of human blood vessels and renal organoids [204]. Because the Suppressive effects of this molecule were incomplete, it was previously thought that the virus might use a second receptor or another agent such as TMPRSS2 [87]. For this purpose, TMPRSS2 inhibitors were authorized for clinical utilization in COVID-19 to prevent virus entry [202]. Thus, Suppression of protease activity required for the degradation of viral spike proteins: For example, Suppression of the enzymatic activity of TMPRSS2 could serve as other new therapeutic option. This could potentially suppress viral interaction via the receptor and its entry into cells [48].

5.11.2. Induction of the downstream pathway of ACE2

Binding of coronavirus spike protein to ACE2 is hypothesized to lead to the destruction of this receptor by various proteases and the lack of protective function of the ACE2/MAS axis in the body organs. Additionally, activation of the classical pathway (ACE/RAS/Ang II) and alternative pathways through tissue-specific proteases, such as chymase-like proteases and cathepsins, leads to high production of Ang II in tissue. This process may alter the balance of the protective function of Ang (1-7)/MAS and ACE2 to the destructive effects of increment Ang II, leading to epithelial and endovascular lung damage. Thus, activating the ACE2/Ang1-7/MAS axis, which induces the downstream pathway of ACE2, is likely to be an effective way to prevent lung and cardiovascular damage due to SARS-CoV2 infections [48]. Furthermore, the protective effect of Ang1-7 or its analogs, including AVE0991 AVE0991 (Pinheiro et al., 2004) versus the destructive effects of increment Ang II, is possible and may be beneficial in the treatment of patients with Covid-19 [205].

5.11.3. CD147

CD147 can connect with cyclophilin as a signaling receptor and mediate extracellular CyPA signaling and chemotactic activities [206]. It is reported that during HIV-1 infection, CyPA in host cells carries the fledgling virus through binding to the HIV-1 Gag protein. As the virus matures and the Gag is released, CyPA redistributes at the virus surface and by interacting with protein receptors on the surface of target cells, it mediates HIV-1 adhesion to host cells. The CD147 can spread HIV-1 infection through interaction with virus-associated CyPA. The CD147 molecule acts during SARS-CoV infection through a similar mechanism in HIV-1 infection in host cells: interaction with CyPA. CD147-antagonist Peptide 9, which has a high rate of binding to HEK293 cells, has a suppressive effect on SARS-CoV. Due to the similarity of SARS-CoV and SARS-CoV-2 characteristics, a study examined the possible function of CD147 in the entry of the virus into host cells. This study showed that CD147 plays an important role in the spread of infection of host cells with the virus, so that inhibition of CD147 on host cells suppresses SARS-CoV-2. Surface plasmon resonance confirmed the interaction between S protein and CD147 [207]. CD147 has been shown to be involved in the infection of host cells by SARS-CoV with the help of CyPA binding to the N protein of SARS-CoV [2,208]. Clinical trials have shown that the use of CD147 antibodies such as meplazumab improves patients with COVID-19 at an appropriate safety dose [209]. This evidence suggests that CD147 could be a new route for SARS-CoV-2 infection. CyPA, along with CD147, may play an important role in SARS-CoV-2 infection, and CyPA suppressors may block SARS-CoV-2 infection by inhibiting the route of infection [210].

5.11.4. MBL

MBL is a serum C-type lectin that can bind to SARS-CoV and infected cells, as well as inhibiting the virus's infectivity. SARS infection is more likely in people who are "MBL-deficient," according to studies. MBL is a promising therapeutic and preventative method for SARS-CoV-2 pandemics, which we support [211].

6. Conclusion

COVID-19 is an intricate viral disease that stimulates host immune responses. Knowing the different and influential factors in this disease's pathogenesis can help design a suitable drug for its treatment. Factors such as heredity and genetic changes may contribute to the susceptibility and pathogenicity of COVID-19. A thorough understanding of the molecular structures and mechanisms that drive COVID-19 extension is essential to ending the prevalent pandemic and controlling the disease's further spread. This paper discussed the expression levels, variants, and changes in some host genetic factors such as ACE2, TMPRSS2, GRP78, IFITM3, HLA, MBLs, and TLRs. The common and unique polymorphisms in some of these molecules may explain genetic susceptibility to COVID-19 as well as for risk factors such as cancer and high-risk groups of patients. This study briefly showed that polymorphisms in some of these molecules might be associated with genetic susceptibility to COVID-19.

Conflict of interest

The authors declare no conflict of interest.

Funding statement

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