

SARS-CoV-2 Receptors

Subjects: Virology

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Definition

Different host-cell receptors are utilized by viral proteins to recognize host cells, such as integrins, angiotensin-converting enzyme 2 (ACE2), sialic acid receptors, dipeptidyl peptidase 4 (DPP4), and glucose regulated protein 78 (GRP78).

1. Introduction

Human coronaviruses (CoVs) are a new type of virus (order Nidovirales) identified in the mid-1960s and classified taxonomically under Coronaviridae family and Coronavirinae subfamily ^{[1][2]}. Coronaviruses are given this name for the crown-like spikes on their surface and are classified, based on their genetics, into four main groups known as alpha, beta, gamma, and delta coronaviruses. The majority of gamma coronaviruses and delta coronaviruses affect birds, whereas alpha coronaviruses and beta coronaviruses infect rodents and bats ^[3]. There are seven known coronavirus strains that can infect humans: 229E and NL63—alpha coronaviruses; OC43, HKU1, MERS-CoV, SARS-CoV, and the newly identified SARS-CoV-2—beta coronaviruses ^[4]. Sometimes coronaviruses that infect animals can also make people sick and turn into human coronaviruses, as in cases with SARS-CoV, MERS-CoV, and the new SARS-CoV-2 ^{[5][6]}. The infectious bronchitis virus (IBV) was the first CoV discovered, and it primarily infected the respiratory systems of chickens. On the other hand, the first two human coronaviruses identified were HCoV-229E and HCoV-OC43, which cause common cold symptoms in people ^{[7][8]}.

Severe acute respiratory syndrome (SARS), which is a viral respiratory disease caused by a SARS-associated coronavirus (SARS-CoV), was first identified in 2003 during an outbreak that emerged in China and then spread to more than 30 countries, resulting in a fatality rate of nearly 10% (774 deaths out of 9098 cases), turning the world's attention to human coronaviruses ^{[9][10][11]}. Since then, several other HCoVs were identified; nearly 30 strains were found. The first HCoV strain identified was B814 that was isolated in 1965 ^[12]. In the post-SARS era, several other HCoVs strains appeared, including HCoV-NL63 in 2004, HCoV-HKU1 in 2005, and 229E and OC43 between 2003 and 2005 ^[13], which caused mild to moderate upper-respiratory tract illness in humans, resulting in approximately 15–30% of common cold cases ^[8]. Later in 2012, another human coronavirus with a higher fatality rate (35%) invaded the Middle East and spread to other countries, which was then named the Middle East Respiratory Syndrome coronavirus (MERS-CoV) ^{[14][15][16][17]}. Recently, at the end of December 2019, specifically in Wuhan, China, a new coronavirus was discovered in a number of patients suffering from severe pneumonia, resulting in a new disease called coronavirus disease of 2019 (COVID-19), which turned out to be a new type of human coronaviruses and was given the name SARS-CoV-2: severe acute respiratory syndrome coronavirus 2 ^{[18][19][20][21]}.

Different host-cell receptors are utilized by viral proteins to recognize host cells, such as integrins, angiotensin-converting enzyme 2 (ACE2), sialic acid receptors, dipeptidyl peptidase 4 (DPP4), and glucose regulated protein 78 (GRP78).

2. SARS-CoV-2 Entry Receptors and Potential Therapeutic Targets

2.1. TLR1/2/6 in Proinflammatory Responses

The TLR2 receptor, which recognizes bacterial lipopeptides (LP), collaborates to form functional heterodimers with either TLR1 or TLR6 to mediate intracellular signaling ^{[22][23][24]}. TLR2 is regulated in chronic obstructive pulmonary disease (COPD) and predominantly detects invasive Gram-positive bacteria, mycobacteria, and fungi ^{[25][26][27][28]}. TLR2 heterodimers with either TLR1 or TLR6 enhanced

proinflammatory responses during viral infection by identifying viral glycoproteins [29][30]. This implies a limited function for antiviral immunity [31]. The immunopathological functions played by TLR1 and TLR6 during SARS-CoV-2 infection remain to be clarified [30]. However, increased levels of TLR2 with either TLR1 or TLR6 DAMPs, including beta-defensin-3, named TLR1/2, and the high-mobility group box-1 (HMGB1), named TLR1/2/6, were recorded in peripheral blood mononuclear cells and serum obtained from COVID-19 patients [32][33][34]. The direct binding between DAMPs and the corresponding TLRs can trigger TLR-mediated inflammatory reactions, analogous to that induced by PAMP recognition [35]. Consequently, TLR1/2/6 activation and its consequent signal transduction may play a role in explaining the immunopathological symptoms observed by COVID-19 patients in clinical settings.

2.2. SARS-CoV-2 Infection and TLR3 Role in Antiviral Immunity

TLR3 is required for antiviral immunity because it recognizes and communicates with viral PAMPs, such as double-stranded ribonucleic acid (dsRNA) generated by positive sense-strand RNA and DNA viruses during viral replication [36][37], small interference RNA [38], and inadequate stem structures in single-stranded RNA [39]. Liberated cellular debris, besides the cytoplasmic nucleotides (messenger RNA and dsRNA) and GRP78, activates TLR3 DAMPs from host cells [38][40][41]. TLR3 is unique in that it is the only TLR that interacts solely with TRIF, activating both NF- κ B and interferon-regulatory factor-3 and 7 [36]. This interaction causes pro-inflammatory molecules to be released, such as IL-1 β , IL-6, IL-8, and TNF- α , found in the immunopathological screening of COVID-19 patients [42][43]. Direct communication between TLR3 and the SARS-CoV-2 S protein has yet to be explained. TLR3 may recognize SARS-CoV-2 products released during viral replication, indicating that TLR3 may be a therapeutic target that, when activated, may increase antiviral immune responses, decrease viral loads, and promote SARS-CoV-2 blockage [44].

2.3. TLR4 Inhibition and SARS-CoV-2 Entry

TLR4 recognizes lipopolysaccharide (LPS) of bacteria and its activation generally results in the production of chemokines and pro-inflammatory cytokines [45]. Due to the physiological characterization of LPS, the TLR4 receptor is responsible for Gram-negative bacterial immunity [44][46]. TLR4 activation and interaction with viral fusion proteins and glycoproteins, such as those seen in respiratory viruses, have been described [47][48]. TLR4 can react to a variety of DAMPs originating from the host, which have been linked to increased and uncontrolled inflammation in autoimmune illnesses and chronic inflammatory disorders [49][50]. TLR4-mediated inflammation that is unregulated has been associated with immunopathological effects in COVID-19 patients [50]. In computational studies investigating the TLR-binding efficacy of S protein have demonstrated that TLR4 has the highest affinity for the S1 domain of the S protein [51]. As TLR4's ability to suppress pathogens could constitute a novel viral entry route for SARS-CoV-2, TLR4 inhibition as a potential treatment in COVID-19 infection should be examined.

2.4. TLR5 as a Potential SARS-CoV-2 Vaccine Target

During vaccine development and to enhance the vaccine efficacy by tailoring the immune responses, a potent immunomodulatory agent called flagellin, which is a structural whip-like filament dependent on microtubules, has been used as an adjuvant component [52][53] due to its ability to influence pathogenic virulence to enable locomotion in motile Gram-negative and positive bacteria [54][55]. The interaction of flagellin with TLR5 leads to subsequent NF- κ B motivated inflammation through enrolment of MyD88 and has been shown to be an effective immunomodulatory agent [22][56][57][58][59]. The use of flagellin to target TLR5 in the creation of vaccines against viral infections has been studied. However, the interaction of TLR5 with SARS-CoV-2 needs to be investigated. In silico studies showed positive energy for TLR5 and S protein of SARS-CoV-2, indicating a possible association [51].

2.5. TLR7 and TLR8 Role in SARS-CoV-2 Infection

Toll-like receptors 7/8 (TLR7/8) are pattern recognition receptors (PRR) located on intracellular organelles that produce antiviral immunity by recognizing the viral single-stranded RNA (ssRNA) and releasing cytokines, chemokines, IFN- α , IFN- β , and IFN- λ as pro-inflammatory mechanisms [60][61]. Studies have

demonstrated TLR7/8's role in reducing viral replication in HIV-1 [62], influenza [51], and MERS-CoV [63]. When viral ssRNA binds to TLR7/8 upon viral entry, antiviral immunity is activated. The SARS-CoV-2 genome has shown more ssRNA segments that TLR7/8 can detect than the SARS-CoV genome, suggesting SARS-CoV-2 causes innate immune hyperactivation [64]. This observation suggested a strong pro-inflammatory response via TLR7/8 recognition. On the other hand, a larger number of SARS-CoV-2 fragments that TLR7/8 identified suggested that rapid release of type I IFNs by TLR7/8 influences the severity of SARS-CoV-2 by changing dendritic Cell (DC) growth, maturation, and apoptosis, and virus-specific cytotoxic responses produced by T lymphocytes and cytotoxicity of natural killer cells [64]. As DC function has been shown to be reduced, attempts to reverse this negative effect may be effective in Covid-19 treatment [65]. COVID-19 patients showed increased blood levels of pro-inflammatory cytokines and chemokines, which are produced by the TLR7/8 pathways [60]. This could be attributed to an increase in TLR7/8 recognizing antiphospholipid antibodies (aPL) (a TLR7/8 activating DAMP) in COVID-19 patients [43][66][67]. TLR7 and TLR8 activation could be employed to improve viral immunity as a potential therapeutic therapy. Based on data analysis collected from mice models treated with imiquimod following influenza A infection, imiquimod, a dual TLR7/8 agonist, has been proposed as a viable treatment for COVID-19 patients [68]. Direct infusion of imiquimod into the lungs lowers viral multiplication, avoids pulmonary inflammation and leukocyte infiltration; protects against pulmonary dysfunction worsening; and elevates pulmonary immunoglobulins and bronchiole fluid antibodies (such as IgG1, IgG2a, IgE, and IgM) [69]. Due to its role in increasing antigen-specific antibody production and enhancing the immune response for viral clearance, imiquimod could be used both for COVID-19 therapeutic treatment and as an adjuvant in the SARS-CoV-2 vaccine [70][71].

2.6. C-Lectin Type Receptors Involved with SARS-CoV-2

C-type lectin receptors (CLRs) are a large family of transmembrane-soluble pattern recognition receptors that contain one or more conserved carbohydrate-recognition domains [72][73]. Such receptors can help in the calcium-dependent recognition of glycosylation marks present on pathogens' proteins [74]. CLRs interact with mannose, fucose, and glucan mono- and polysaccharide structures to identify infections [75]. PAMP recognition by CLRs results in pathogen uptake, breakdown, and antigen presentation [76]. CLRs can as well connect with other PRRs, such as TLRs, allowing for the strengthening or weakening of innate immunity inflammatory responses by increasing or decreasing receptor activation and signal transduction [77][78]. In vitro study models have demonstrated a direct relationship between selective CLRs and SARS-CoV-2 spike protein mannosylated and N- and O-glycans [79].

3. Conclusions

The coronavirus disease COVID-19, caused by the SARS-CoV-2 virus, spreads mainly through person-to-person contact. SARS-CoV-2 is one of seven identified human coronaviruses that can cause serious illnesses. SARS-CoV-2 can trigger a respiratory tract infection, ranging from mild to deadly, and can cause respiratory failure, septic shock, pneumonia, heart, and liver complications, and may lead to death.

We covered the history and progression of human coronaviruses in this paper and the various host-cell receptors that may be engaged in the viral entry mechanism, showing that the SARS-CoV-2 virus can use multiple receptors to enter the host-cells. Understanding the mechanism of SARS-CoV-2 infection requires determining the pathway through which the virus components bind to host-cell receptors. The information gathered in this study can be used as a guided tool to investigate how different cell types interact with the SARS-CoV-2 virus, while supported experimental investigations are required to explain the susceptibility differences to the viral infection. Afterward, we could ultimately be able to explain why some people are more susceptible to SARS-CoV-2 infection than others. In addition, it could help researchers understand how to specifically target the SARS-CoV-2 virus with drugs and immunotherapies to treat COVID-19 symptoms and improve the vaccine development research pipeline to prevent the disease.

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