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Review Article

Cellular Receptors and their Associated Factors for SARS-CoV-2 Entry Designing Susceptible Cells: A Review

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Abstract
SARS-CoV-2, the causative agent of COVID-19, emerged in late 2019 and rapidly evolved into a significant global health crisis, impacting millions of individuals worldwide. Like other respiratory viruses, SARS-CoV-2 depends on specific cellular receptors to infiltrate host cells and initiate the infection process. To effectively combat this virus, it is essential to thoroughly understand the intricate interactions between viral attachment factors and these cellular receptors. This analysis explores the various cellular receptors involved in the infection process of SARS-CoV-2 and examines the complex interactions between the virus and its host cells. We emphasize the critical components that facilitate the virus's entry into host cells and consider potential strategies to modify receptor expression, thereby enhancing susceptibility to infection. Gaining insights into these receptors and their associated components is vital for developing effective animal models, which can significantly aid in research efforts. Ultimately, this understanding will contribute to the creation of targeted therapeutic interventions and preventive measures against COVID-19 and similar viral infections.

Keywords: Cellular Receptors, Respiratory Viruses, SARS-Cov 2, Susceptible Cells
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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a positive-sense RNA virus enclosed in a lipid membrane and uses a highly glycosylated spike (S) protein for attachment, membrane integration, and entry into host cells. The S protein is classified as a class I insertion polypeptide and consists of 1,273 amino acids and has a homotrimeric structure. Each monomer consists of two subunits, S1 and S2, which contain three topologically distinct domains: a head,[1] a central stalk, and a cytoplasmic tail.[2] The S1 subunit, known as the receptor-binding domain, consists of a N-terminal domain (NTD) and a receptor-binding domain (RBD). In contrast, the S2 subunit, known as the membrane-integration domain, contains an insertion peptide (FP) and two heptad repeats (HR1 and HR2), which are essential structural elements in the membrane-integration process.[3] The following happens in this process:

1. The initial stages of infection begin when the receptor-binding domain in the S1 subunit specifically binds to the peptidase domain of the receptor responsible for cell entry, called angiotensin-converting enzyme 2 (ACE2).[4,5]

2. The S protein is cleaved at two distinct points. The first cleavage occurs at the junction of the S1 and S2 subunits, where a transforming protein called furin cleaves the RBD from the fusion domains.[3]

3. Subsequent cleavage at the S2′ site occurs after interaction with ACE2 and involves cellular proteases such as TMPRSS2 or CTSL (Transmembrane serine protease-2 and Endolysosomal cathepsin-L). This mechanism increases the prominence of the fusion peptide and aids in the integration of the virus with the host cell membrane.[3,4,6,7]

Studies have shown that Neuropilin-1, also known as NRP1, is known for its ability to bind to furin-cleaved substrates and has been shown to associate with the furin-cleaved S1 protein. This association aids in viral entry via endocytosis, thereby enhancing the infectivity of SARS-CoV-2.[8] Also, additional receptors that may serve as alternative entry points for SARS-CoV-2 into cells have been identified. These include CLEC4G, AXL, CD147, CD209 (CLEC4M), KREMEN1 and ASGR1.[3,9] Many viruses can infect only certain cells in specific hosts. These 'susceptible hosts' have

the receptors that viruses need to attach and enter the cells. Therefore, research usually focuses on identifying cell lines that are best suited for virus replication, allowing researchers to effectively monitor the phenomena under study.[9]

SARS-CoV-2 Cellular Receptors and their Associated Factors

The entry of SARS-CoV-2 into host cells is a multistep process involving a complex interplay between the viral spike (S) protein and various host cell receptors. A critical step in this process is the binding of the S1 subunit of the spike protein to the primary receptor, ACE2, on the cell surface. This interaction is mediated by the receptor-binding domain (RBD) of the spike protein and triggers conformational changes in the spike structure, ultimately leading to the exposure of the S2′ site and facilitating subsequent proteolytic cleavage. Following ACE2 engagement, the spike protein undergoes cleavage at two essential sites, including:

- The S1/S2 site, which is cleaved by the host cell protease furin during viral protein synthesis in the producing cell.
- The S2′ site, which is cleaved by host cell surface proteases such as TMPRSS2 or by endosomal proteases like cathepsin L (CTSL) in the target cell.

These cleavage events activate the fusion peptide, enabling the fusion of the viral envelope with the host cell membrane and allowing the viral RNA genome to enter the cytoplasm.[3,10-12] In addition to ACE2, several other receptors and co-factors contribute to or enhance viral entry, including Neuropilin-1 (NRP1), KREMEN1, DC-SIGN, L-SIGN, ASGR1, AXL, CD147, SR-B1, GRP78, and others (Figure 1). Many of these molecules facilitate either the endocytic or membrane fusion pathways of viral entry or influence the susceptibility of different cell types to infection. Moreover, several of these factors represent potential therapeutic targets for antiviral interventions.[3,13,14] Notably, the entry pathways of SARS-CoV-2 can vary depending on the cell type and the presence of specific proteases. Viral entry may occur either at the cell surface (plasma membrane) or via the endosomal route. For instance, in cells lacking TMPRSS2, viral entry is predominantly mediated through endocytosis followed by activation by cathepsins.[15,16] Some of the most important of these molecules and factors are introduced below.

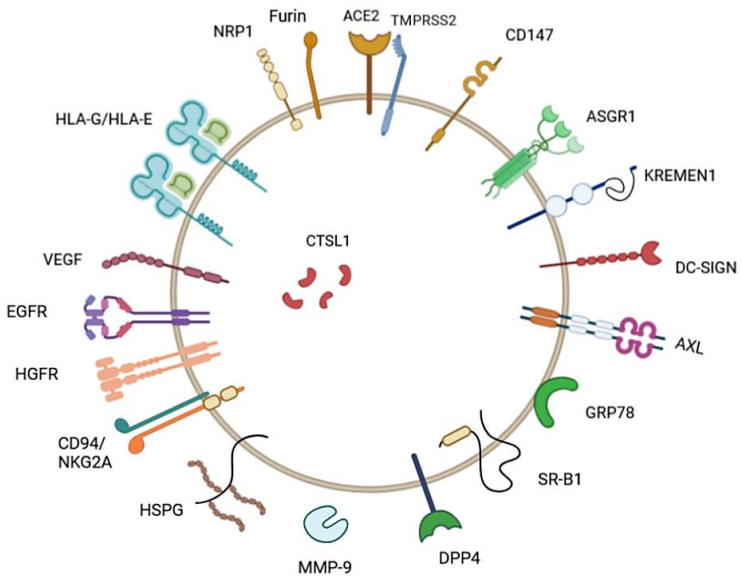

Figure 1. Overview of Receptors and their Associated Factors Facilitating SARS-CoV-2 Cell Entry Include: ACE2 (Angiotensin-converting enzyme 2), CD147, AXL (AXL receptor tyrosine kinase), KREMEN1, ASGR1 (Kringles Containing Transmembrane Protein 1 and Asialoglycoprotein receptor 1), CD209 (CLEC4M)/CLEC4G (C-type lectin domain family 4 member M/G), NRP1 (Neuropilin-1), DPP4 (Dipeptidyl peptidase 4), HLA-G/HLA-E (human leukocyte antigens G/A/E), VEGF/EGFR/HGFR (Vascular endothelial growth factor/Epidermal growth factor receptor/Hepatocyte growth factor receptor), MMP-9 (Matrix metalloproteinase-9), FURIN, CTSL1 (Cathepsin L1), SR-B1 (Scavenger receptor class B type 1), HSPG (Heparan Sulfate Proteoglycans), TMPRSS2 (Transmembrane serine protease 2), CD94/NKG2A (Natural killer group 2 member A), and GRP78 (Glucose-Regulated Protein 78).

ACE2

ACE2 is mainly located in the kidneys, heart, and testes, and is widely distributed in the lungs, liver, intestines, and brain. The lungs are the main organ affected by SARS-CoV-2 infection. A study of single-cell RNA sequencing data from 43,134 human lung cells showed that 0.64% of these cells express ACE2, and that 83% of ACE2 is localized to the apical surface of alveolar type II epithelial cells (AT2).[17] ACE2 is found on the X chromosome, specifically in the Xp22 region. The gene consists of 18 exons and 20 introns,

which results in six different forms through alternative splicing.[18] ACE2 is found in two distinct forms. The full-length mACE2 is located on the membrane of cells and contains a membrane anchor and an extracellular domain that acts as a receptor for the spike (S) proteins of the SARS-CoV-2 virus. These spike proteins are divided into two subunits, S1 and S2, and the interaction between the S1 protein and the receptor is essential for the virus's ability to infect host cells. The second form, known as sACE2, is a soluble form that is present in the bloodstream. When SARS-CoV-2 binds to ACE2, it initiates a process called receptor-dependent internalization. Notably, ACE2 plays an important protective role in tissues during severe acute lung injury. Furthermore, differences in sACE2 levels among COVID-19 patients indicate that adults and men typically have higher plasma levels of sACE2 than children and women.[18-20]

CD147

CD147, an adhesion molecule, is known to be an essential element in regulating inflammatory and immune responses.[21] CD147, also known as basigin or EMMPRIN, is a glycoprotein that crosses cell membranes and is part of the large immunoglobulin family. This molecule is involved in tumor development, Plasmodium invasion, and infections caused by bacteria and viruses.[22] CD147 is widely expressed in various human tissues and is involved in many natural and disease-related processes due to its many interactions. This molecule plays an important role in infections caused by HIV-1, hepatitis B virus (HBV), hepatitis C virus (HCV), and Kaposi's sarcoma-associated herpesvirus (KSHV).[23,24] At the end of 2020, Wang et al. were the first to discover the interaction between the SARS-CoV-2 virus spike protein and the CD147 receptor on host cells. They showed that changes in the level of this receptor affect the ability of the virus to infect target cells. Furthermore, their results showed that the CD147 receptor is involved in the infection of immune cells that do not express ACE2, introducing this pathway as a possible new route of virus entry.[22,23,25] CD147 acts as a signaling mediator and is implicated in cytokine storm syndromes (CSSs) seen in severe cases of COVID-19. This role is due to its ability to regulate CyPA expression.[26]

AXL (AXL Receptor Tyrosine Kinase)

AXL is a receptor that functions as a tyrosine-protein kinase. The protein was originally called UFO due to its undetermined function as a protein associated with tumorigenic properties.[27] AXL (anexelekto) has been identified as a novel therapeutic target in the human cell membrane. It has been suggested that this mechanism may provide an alternative route for SARS-CoV-2 to enter cells through interaction with the viral S protein, independent of ACE2.[28] In 2020, Wang and colleagues noted that increasing AXL levels in HEK293T cells facilitated virus entry and its efficacy was similar to ACE2. They also highlighted that reducing AXL levels, while leaving ACE2 levels unchanged, significantly reduced the rate of infection of lung cells by the SARS-CoV-2-like virus.[29] In a related study conducted in 2021, researchers discovered that the protein tyrosine kinase receptor UFO (AXL) specifically interacts with the N-terminal region of the SARS-CoV-2 spike protein. Their study, which included a SARS-CoV-2 pseudovirus and the actual virus, showed that overexpression of AXL in HEK293T cells enabled SARS-CoV-2 entry at levels similar to those achieved by overexpression of ACE2. In contrast, the absence of AXL significantly reduced the rate of SARS-CoV-2 infection in H1299 lung cells as well as in primary human lung epithelial cells.[30]

KREMEN1 and ASGR1

The researchers found that the cellular proteins ASGR1 and KREMEN1 interact with the S protein. When they expressed ASGR1 and KREMEN1 in a cell line that lacked ACE2, they enabled SARS-CoV-2 to enter the cells, while SARS-CoV was unable to do so.[31] KREMEN1 is present in several tissues, including the brain, esophagus, endocrine and reproductive organs, and skin, where it negatively regulates Wnt signaling. Asialoglycoprotein receptor-1 (ASGR1, CLEC4H1), a calcium-dependent C-type lectin receptor, is found primarily in hepatocytes. Both receptors have a high affinity for the RBD and interact with the NTD. Research suggests that KREMEN1 and ASGR1 can facilitate viral entry in the absence of ACE2, even in cells and mouse models that do not express ACE2.[4,27,32]

CD209 (CLEC4M)/ CLEC4G

C-type lectin receptors (CLRs) such as DC-SIGN/CD209 and L-SIGN/CD209L/CLEC4M are frequently present in the human immune system, particularly on monocytes, dendritic cells, and macrophages. These receptors are essential as a first line of defense against viruses and other invading pathogens.[33] C-type lectin proteins, particularly CD209/DC-SIGN and CD209L/L-SIGN, function as specific receptors that are critical for cell adhesion and pathogen recognition. These proteins mediate cell-cell interactions and are capable of recognizing a wide variety of pathogens, including viruses such as SARS and SARS-CoV-2, as well as bacteria, parasites, and fungi. Human coronaviruses, including NL63, CoV-229E, OC43, MERS-CoV, HKU1, SARS-CoV, and SARS-CoV-2, use an evolutionary conserved mechanism to recognize host cells. This mechanism relies on the interaction of the viral spike (S) glycoprotein with specific receptors located on the surface of target host cells.[34,35] Due to the similarity of spike proteins among coronaviruses, SARS-CoV-2 can enter host cells in a similar way to SARS-CoV. The virus uses three different receptors: ACE2, DC-

SIGN (also known as CD209), and L-SIGN (also known as CLEC4M).[36,37] CLEC4G, also known as LSECtin, is a C-type lectin domain protein that is likely related to the SARS spike protein. It is believed to act as an adhesion factor and enhance viral infection.[38,39]

Neuropilin-1 (NRP1)

Neuropilin 1 (NRP1) is one of the two homologous NRPs found in all vertebrates, playing significant roles in both physiological and pathological processes.[40] NRP1 acts as a mediator or cellular receptor that, together with ACE2 and TMPRSS2, helps SARS-CoV-2 enter host cells, increasing its infectivity and influencing its susceptibility. In addition, NRP1 is known to facilitate infection of host cells by other viruses, including Epstein-Barr virus (EBV).[41] NRP1 is widely found in the respiratory and olfactory regions, particularly in endothelial and epithelial cells lining the nasal cavity. Autopsy neuropathology studies of COVID-19 patients have shown that SARS-CoV-2 attacks NRP1-expressing cells in the olfactory epithelium and olfactory bulb.[42,43]

HLA-G/HLA-E

The immune response to pathogens is influenced by a set of genetic factors that determine an individual's susceptibility or resistance to infections caused by viruses, fungi, bacteria, and parasites. Specifically, these factors are linked to genes in the human leukocyte antigen (HLA) system, which is located on the short arm of chromosome 6 in humans.[44] HLA molecules exhibit significant polymorphism and are crucial in determining an individual's genetic susceptibility to various human diseases, particularly those caused by infectious agents.[45] HLA-E and HLA-G are non-classical molecules renowned for their ability to promote immune tolerance.[46] Viruses use HLA-G and E molecules to modulate the host immune response. In addition, these molecules may also be involved in regulating inflammatory responses caused by viral infections.[47] HLA-G expression has been detected in various pathological conditions, such as cancer and viral infections.[48] HLA-G levels may increase in response to various viral infections, including SARS-CoV-2. This increase can lead to significant immunosuppressive effects, helping the virus evade immune system recognition and facilitating disease progression.[49] Research has shown that SARS-CoV-2 can trigger the expression of HLA-E on lung epithelial cells. It's been suggested that CD8+ T cells restricted by HLA-E could be used to treat patients with severe COVID-19 during the early stages of infection.[50]

CD94/NKG2A

Natural killer (NK) cells are a type of lymphocyte that originates from the same progenitor lineage as B and T cells, but they function nonspecifically and are therefore considered components of the innate immune system. These cells play a critical role in the recognition and destruction of virally infected and tumor cells. MHC class I molecules are usually reduced or altered by these cells to prevent activation of the immune response.[51] NKG2x/CD94 receptors (where x represents A, C, or E) located on natural killer cells are critical for immune surveillance because they interact with HLA-E complexes. These complexes present peptides specifically from MHC class I leader sequences and help assess MHC class I expression levels.[52] Recent research has pointed to the critical role of NKG2A in SARS-CoV-2 infections. In patients with COVID-19, a significant increase in NKG2A expression was observed in peripheral natural killer cells and CD8+ T cells, which was associated with more severe disease complications.[53]

Dipeptidyl Peptidase 4 (DPP4)

Dipeptidyl peptidase 4 (DPP4) was first identified in 1966. It is commonly referred to as the T-cell activation antigen CD26 or as adenosine deaminase binding protein (ADBP).[54] New findings show that SARS-CoV-2 binds to DPP4/CD26 upon entry into respiratory tract cells. The co-existence of ACE2 and DPP4/CD26 as receptors for spike glycoproteins suggests that different types of human coronaviruses may target similar cells in different tissues, which could explain the similar clinical symptoms seen in patients infected with different types of coronaviruses.[55] The interaction between the MERS-CoV spike protein and DPP4 involves not only the RBD in domain B of the S1 subunit but also interactions from domain A with sialylated receptors, aiding viral entry into airway epithelial cells.[56]

VEGF/EGFR/HGFR

The VEGF family comprises eight members: VEGF-A to F, placental growth factor (PlGF), and endocrine gland-derived VEGF (EG-VEGF).[57] The progression of COVID-19 often involves the overproduction of cytokines and inflammatory mediators. VEGF, which is essential for vascular permeability and inflammation, is significantly increased in the blood of COVID-19 patients and correlates with disease severity.[58] VEGF plays an important role in COVID-19 progression and is associated with pulmonary edema, decreased oxygen saturation, and changes in vascular structure. Damage to the integrity of the alveolar-capillary membrane leads to fibrin accumulation, which plays a role in the fibroproliferative phase associated with acute respiratory distress syndrome (ARDS).[59] A preclinical model analysis revealed that SARS-CoV-2 exhibits a high affinity for the VEGFR, EGFR, and c-MET (HGFR) receptors on glial cells, which are closely linked to glioma development.[60] Growth factor receptor (GFR) signaling is critical in cancer progression and plays a key role in the mechanisms of infection of certain viruses. Activation of GFRs affects various cellular activities, including proliferation, adhesion,

and differentiation. Viruses such as Epstein-Barr, hepatitis C, and influenza use the epidermal growth factor receptor (EGFR) to enter cells. In addition, activation of GFR signaling may also be essential for respiratory viruses, including SARS-CoV-2.[61,62] c-Met (cellular-mesenchymal epithelial transition factor), also referred to as the hepatocyte growth factor receptor (HGFR), stands out as a distinct member of the receptor tyrosine kinase (RTK) family.[63] In 2020, Khan and colleagues showed that Hex docking results revealed the SARS-CoV-2 spike (S) protein binds to VEGFR, EGFR, and c-MET receptor proteins with a similar affinity as its binding to ACE2.[64] Recent studies have provided increasing evidence of the involvement of VEGF and EGFR signaling pathways in the vulnerability of respiratory cells to viruses. Activation of the VEGF receptor (particularly VEGFR-2) can stimulate multiple pathways such as Raf-MEK-ERK and PI3K/Akt in epithelial cells, which lead to increased vascular permeability, inflammation, and even enhanced entry and replication of certain viruses, including poxviruses and RSV.[65,66] In SARS-CoV-2 infection, the interaction between the VEGFR-2/NRP-1 complex and the binding of the viral S protein to NRP-1 can disrupt signaling balance, enhance the release of VEGF-A, and promote the activation of the VEGFR-1 receptor on immune cells, ultimately exacerbating inflammation and disease progression.[67] On the other hand, activation of the EGFR receptor by viruses such as Influenza and RSV stimulates the ROS/MAP kinase pathways and inhibits the production of interferon-λ (IFN-λ) by suppressing the regulatory factor IRF1. This mechanism weakens the innate antiviral defense of the epithelium and enhances viral replication.[68,69] Moreover, stimulation of EGFR and activation of the MAPK/ERK pathway lead to increased cytokine production and enhanced cell adhesion, which can both facilitate viral replication and, in some cases, be associated with suppression of the antiviral response.[70] Nevertheless, some conflicting evidence has highlighted the complex role of these receptors; for example, data from animal models often fail to clearly distinguish between the protective and pathogenic roles of VEGF or EGFR signaling, as immune responses, lung development, and receptor expression in animals differ from those in humans.[71,72] Furthermore, the success of certain targeted therapies against these pathways in animal models has not necessarily been replicated in human studies, highlighting the limitations of translating data from animal models to clinical settings.[72]

MMP-9

Research shows that MMP-9 is significantly released by neutrophils and monocytes in respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and lung fibrosis, where extracellular matrix (ECM) remodeling occurs. In cases of severe lung injury, inflammation is stimulated by increased activity of MMP-9 (gelatinase-B with a molecular weight of 92 kDa), which leads to the breakdown of the alveolar capillary barrier and contributes to the migration of inflammatory cells, ultimately leading to lung tissue damage.[73] Recent research has revealed an elevated expression of the metalloproteinases-9 (MMP-9) gene in COVID-19 patients. Immunoassays show that MMP-9 levels are directly correlated with an increased risk of respiratory failure.[74,75]

FURIN

Furin is a type 1 membrane-associated protease that aids in the entry of SARS-CoV-2 into endothelial cells.[76] SARS-CoV-2 has a specific furin cleavage site (PRRAR) in its spike protein that is not present in other group 2B coronaviruses. Previous structural studies have shown that furin cleavage enhances the binding of additional S protein to the human ACE2 receptor, which may contribute to the emergence of the virus in humans.[77]

CTSL1

Cathepsin L (CTSL), which belongs to the family of lysosomal cysteine proteases, features an L domain composed of α-helices and an R domain made up of β-sheets within its three-dimensional structure.[78] CTSL is produced by tumor tissues and encodes a lysosomal cysteine proteinase that is involved in cancer progression and aids in the entry of SARS-CoV-2. This protein belongs to the C1 peptidase family, which is defined by disulfide-linked dimers composed of heavy and light chains. CTSL is able to proteolytically cleave the S1 subunit of the SARS-CoV-2 spike protein, a necessary step for the virus to enter host cells.[79]

TMPRSS2

Additionally, SARS-CoV-2 uses the same cellular receptor as SARS-CoV (ACE2) to enter cells. It has also been found that TMPRSS2 is necessary for activating the viral spike protein.[80] This suggests that detecting the expression of ACE2 and TMPRSS2 in human tissues may help forecast which cells could be infected and their potential effects in patients with COVID-19.[81] The spike (S) protein of the SARS-CoV-2 virus binds to ACE2 and acts as a receptor for entry. Following this interaction, the transmembrane protease serine 2 produced by TMPRSS2 activates the S protein and facilitates its entry into the cell.[82]

SR-B1

SR-B1 is a receptor present on the surface of cells that helps in the selective uptake of cholesterol esters and various lipid components from HDL particles that bind to this receptor. A 2020 study by Wei et al. showed that reducing SR-B1 levels significantly reduced the binding of actual SARS-CoV-2,

while increasing SR-B1 expression resulted in a significant increase in viral entry into cells.[83] SARS-CoV-2 effectively enters cells when the target cell plasma membrane contains high levels of cholesterol. Recent research suggests that cholesterol movement through scavenger receptor type B-1 (SR-B1), a high-affinity receptor for cholesterol-rich HDL, is critical for virus entry into cells.[84,85]

GRP78

Cells respond to endoplasmic reticulum (ER) stress by initiating an unstable protein response, which results in the production of molecular chaperones to help fold proteins and reduce protein synthesis. Glucose-regulated protein 78 (GRP78), also known as immunoglobulin binding protein (BiP), is a chaperone of the HSP70 family that is encoded by the HSPA5 gene. In response to ER stress, GRP78 can be translocated to the cell surface, which may occur during certain viral infections or cancers or due to its overexpression. Research suggests that when respiratory cells are stressed, they produce high levels of GRP78, which is transported from the endoplasmic reticulum to the cell membrane. The presence of GRP78 on the cell surface contributes to the infection process for viruses including MERS-CoV, dengue, Ebola, Borna disease virus (BDV), Japanese encephalitis virus, and Coxsackie virus A9 (CAV9). Furthermore, increased GRP78 expression is associated with severe COVID-19 risk factors such as advanced age, obesity, diabetes, and lung cancer.[1, 86-89]

HSPG (Heparan Sulfate Proteoglycans)

HSPGs, also known as heparan sulfate proteoglycans, are a type of glycoprotein found on the surface of mammalian cells. These molecules are critical for the efficient binding of viruses to the cell surface, and this interaction significantly contributes to the infection process. Binding to HSPGs has been observed with a variety of viruses, including MHV, SARS-CoV, herpes simplex virus (HSV), cytomegalovirus, hepatitis E virus, dengue virus, and porcine epidemic diarrhea virus (PEDV).[90,91] A number of viruses need to interact with heparan sulfate proteoglycans (HSPGs) on the cell surface to successfully enter and infect their target cells. This group includes various coronaviruses, such as human coronavirus NL63 (HCoV-NL63) and SARS-CoV-2. The spike (S) protein of SARS-CoV-2 binds to HSPGs.[92]

Designing Susceptible Animal Models for SARS-Cov 2

Animal models are of great importance in the study of infectious diseases. For this reason, the scientific community quickly began efforts to find suitable species after the emergence of SARS-CoV-2. Various animals previously used in SARS-CoV research, including mice, sea otters, hamsters, and nonhuman primates (NHPs), have been evaluated as possible models for SARS-CoV-2 infection.[93] Valid animal models for COVID-19 are critical for investigating various aspects of disease mechanisms, supporting drug discovery, and developing effective and safe vaccines. Existing models for SARS-CoV-2 can be divided into two main categories: a) natural models and b) genetically modified models, which exhibit varying levels of vulnerability to SARS-CoV-2 and demonstrate tissue damage in the respiratory tract and other organ systems.[94] Existing mouse models for COVID-19 are critical for investigating factors that influence inflammatory responses and disease resulting from SARS-CoV-2 infection. However, these models typically rely on fixed inbred strains that cannot adequately capture the variability in patient outcomes and the role of host genetics in SARS-CoV-2 infection and treatment responses.[95] Previous research has shown that SARS-CoV-2, like SARS-CoV, binds to the hACE2 receptor. Animals such as cats, dogs, and sea otters can be infected with SARS-CoV-2, although their ACE2 receptor sequences differ. Studies have shown that the human ACE2 receptor has the highest binding affinity for SARS-CoV-2 compared to other species. These differences should be taken into account in animal studies focusing on SARS-CoV-2 infections.[96] Wild mice cannot support SARS-CoV-2 replication because their ACE2 receptors do not match the virus's spike protein. For this reason, scientists have developed genetically modified mice that express human ACE2 (hACE2) on the surface of their cells, allowing the virus to replicate.[97]

Conclusion

The binding between viruses and their receptors is crucial for defining the host range of viruses and understanding their pathogenic mechanisms. The viral binding protein acts as a “key” that allows viruses to gain access to host cells by binding to the “lock,” which represents receptors on the cell membrane. These interactions are essential for the successful entry of viruses into host cells. Understanding the nature of these receptors and the factors associated with them is crucial for the development of effective animal models.

Authors’ Contributions

The resource and writing-original draft preparation were carried out by HEG, SKA, and MRH. The writing review and editing were performed by HEG, SKA, AY, YT, MMN, ASJ and MEM. The supervision was done by HEG. The whole manuscript was read and approved by all authors.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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