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Corona Virus: A Review Article to Identify Novel Drug for Treatment

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Abstract: ***Corona viruses are a group of related viruses that cause diseases in mammals and birds. In humans, coronaviruses cause respiratory tract infections that can be mild, such as some cases of the common cold (among other possible causes, predominantly rhinoviruses), and others that can be lethal, such as SARS, MERS, and COVID-19. Symptoms in other species vary: in chickens, they cause an upper respiratory tract disease, while in cows and pigs they cause diarrhea. There are yet to be vaccines or antiviral drugs to prevent or treat human corona virus infections.***

Keywords: corona virus, ACE2, Hemagglutinin esterase, Protonation, ACE Inhibitor, Angiotension II receptor blocker

1. Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2),[1][2] previously known by the provisional name 2019 novel corona virus (2019-nCoV),[3][4][5] is a positive-sense single-stranded RNA virus.[6] It is contagious in humans and is the cause of the ongoing pandemic of coronavirus disease 2019 (COVID-19) that has been designated a Public Health Emergency of International Concern by the World Health Organization (WHO).[7][8]

The strain was first discovered in Wuhan, China, so it is sometimes referred to as the "Wuhan virus" or "Wuhan corona virus".[14][15][16][17] Because the World Health Organization discourages the use of names based upon locations[12][18][19]and to avoid confusion with the disease SARS,[20] it sometimes refers to the virus as "the virus responsible for COVID-19" or "the COVID-19 virus" in public health communications.[21] The general public often call both the virus and the disease "coronavirus", but scientists and most journalists typically use more precise terms.[22]

Human-to-human transmission of SARS-CoV-2 has been confirmed during the 2019–20 coronavirus pandemic.[8] Transmission occurs primarily via respiratory droplets from coughs and sneezes within a range of about 2 metres (6.6 ft).[23][24] Indirect contact via contaminated surfaces is another possible cause of infection.[25] Preliminary research indicates that the virus may remain viable on plastic and steel for up to three days, but does not survive on cardboard for more than one day or on copper for more than four hours;[26] the virus is inactivated by soap, which destabilizes its lipid bilayer.[27][28] Viral RNA has also been found in stool samples from infected people.[29]

Whether the virus is infectious during the incubation period is uncertain.[30] On 1 February 2020, the World Health Organization (WHO) indicated that "transmission from asymptomatic cases is likely not a major driver of transmission".[31] However, an epidemiological model of the beginning of the outbreak in China suggested that "pre-symptomatic shedding may be typical among documented infections" and that subclinical infections may have been the source of a majority of infections.[32]

Morphology of virus:
Coronaviruses are large pleomorphic spherical particles with bulbous surface projections.[33] The diameter of the virus particles is around 120 nm.[34] The envelope of the virus in electron micrographs appears as a distinct pair of electron dense shells.[35]

The viral envelope consists of a lipid bilayer where the membrane (M), envelope (E) and spike (S) structural proteins are anchored.[36] A subset of coronaviruses (specifically the members of betacoronavirus subgroup A) also have a shorter spike-like surface protein called hemagglutinin esterase (HE).[37]

Hemagglutinin esterase (HEs)
Hemagglutinin esterase (HEs) is a glycoprotein that certain enveloped viruses possess and use as invading mechanism. HEs helps in the attachment and destruction of certain sialic acid receptors that are found on the host cell surface.[38] Viruses that possess HEs include Influenza C virus, toroviruses, and corona viruses. HEs is a dimer transmembrane protein consisting of two monomers, each monomer is made of three domains. The three domains are: membrane fusion, esterase, and receptor binding domains.

The different HEs enzyme activities include: receptor binding activity, receptor hydrolysis (esterase) activity, and membrane fusion activity. The receptor binding activity involve the attachment of HEs to N-acetyl-9-O-acetylneuraminic acid (9-O-Ac- Neu5Ac) of glycolipids and glycoproteins and in turn serve as viral receptor.[39] Receptor hydrolysis (esterase) activity allows virus particles to escape the infected cell by removing an acetyl group from the C9 position of terminal 9-O-Ac-Neu5Ac residues.[2]Membrane fusion activity helps in incorporation viral genome into the host cell cytoplasm by enhancing the attachment between the viral envelope and host cell membrane.

Receptor binding activity:
Glycolipids and glycoproteins contain N-acetyl-9-O-acetylneuraminic acid (9-O-Ac- Neu5Ac) that serve as viral receptor in which HEF binds to. HEF can bind to its receptor whether or not 9-O-Ac-Neu5Ac is attached by an α-2,3 or α-2,6 linkage to the next galactosyl residue. However, host specificity can be affected by terminal N-acetylneuraminic

acid (Neu5Ac) and the glycosidic linkage of Neu5Ac. Influenza C virus can recognize 9-O-Ac-Neu5Ac on the surface of different cells due to its unique receptor specificity.[40]

Receptor hydrolysis (esterase) activity:
The receptor hydrolase activity of HEF aids in the release of virus particles from an infected cell using esterase enzyme that cleaves acetyl from the C9 position of terminal 9-O-Ac-Neu5Ac. The esterase activity of HEF which is part of serine hydrolase class includes a nucleophilic attack of the hydroxyl group (OH) of a serine amino acid, with the help of two other amino acids (histidine and aspartic acid), on the carbonyl group of the substrate. Basic histidine enhances the reactivity of serine by polarizing and deprotonating its hydroxyl group. Along with that, aspartic acid polarizes histidine.[40]

X-ray crystallography of the crystalline structure of HEF showed that serine 57, aspartic acid 352 and histidine 355 are the important amino acids for the esterase activity. Also, early studies showed that mutation in Ser57 and His355 residues can completely stop the esterase activity of HEF.[40]

Membrane fusion activity:
The membrane fusion activity between, the viral envelope and endocytic vesicles of host cell, is important to help the virus inject their genome into the cytoplasm of the cell. In order to activate membrane fusion, Cleaving the precursor proteins HEF0 and HA0 into the subunits into the subunits HEF1 and HEF2, then exposing these proteins to acidic pH must be done prior.[40]

Acidic pH causes protonation of specific amino acids that initiate certain rearrangement of the proteins. The protonated amino acid is found to be histidine while its pKa matches the pH of endosome. Studies showed that there is about 0.7 difference in the pH value that trigger the membrane fusion activity from strain to strain of both influenza A and C.[40]

Conformational change in HEF structure that occur at low pH results in the separation of fusion peptide from its location at the lower part of the stalk and exposing the outer surface of the molecule, so it can be inserted into the endosomal membrane. Another conformational change occur which cause the bending of the ectodomain to push the fusion peptide toward the transmembrane region. As a result of that, the virus and endosomal membranes get closer, exchanging lipids withhemifusion.Then, opening of a fusion pore and eventually complete merger of both lipid bilayers.[40]

Protonation:
In chemistry, protonation (or hydronation) is the addition of a proton (or hydron, or hydrogen cation), (H^+) to an atom, molecule, or ion, forming the conjugate acid.[41] Some examples include
the protonation of water by sulfuric acid:
$H_2SO_4 + H_2O \rightleftharpoons H_3O^+ + HSO^-_4$
the protonation of isobutene in the formation of a carbocation:
$(CH_3)_2C{=}CH_2 + HBF_4 \rightleftharpoons (CH_3)_3C^+ + BF^-_4$

Protonation is a fundamental chemical reaction and is a step in many stoichiometric and catalytic processes. Some ions and molecules can undergo more than one protonation and are labeled polybasic, which is true of many biological macromolecules.

Entry in cell:
Infection begins when the viral spike (S) glycoprotein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelop with the host membrane.[42]

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm.[43] The coronavirus RNA genome has a 5′ methylated cap and a 3′ polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation.[44] The host ribosome translates the initial overlapping open reading frame of the virus genome and forms a long polyprotein. The polyprotein has its own proteases which cleave the polyprotein into multiple nonstructural proteins.[46]

Replication:
A number of the nonstructural proteins coalesce to form a multi-protein replicase-transcriptase complex (RTC). The main replicase-transcriptase protein is the RNA-dependent RNA polymerase (RdRp). It is directly involved in the replication and transcription of RNA from an RNA strand. The other nonstructural proteins in the complex assist in the replication and transcription process. The exoribonuclease non-structural protein, for instance, provides extra fidelity to replication by providing a proofreading function which the RNA-dependent RNA polymerase lacks.[45]

Release:
The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number of accessory proteins.[46] RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment.

Angiotensin converting enzyme 2:
Angiotensin converting enzyme 2 (ACE2)[47] is an enzyme attached to the outer surface (cell membranes) of cells in the lungs, arteries, heart, kidney, and intestines.[48][49] ACE2 lowers blood pressure by catalysing the cleavage of angiotensin II (a vasoconstrictor peptide) into angiotensin 1–7 (a vasodilator).[50][51][52] ACE2 also serves as the entry point into cells for some coronaviruses.[47]

ACE2 counters the activity of the related angiotensin-converting enzyme (ACE) by reducing the amount of angiotensin-II and increasing Ang(1-7)[53] making it a promising drug target for treating cardiovascular diseases.[54][55]

ACE2 is a single-pass type I membrane protein, with its enzymatically active domain exposed on the surface of cells in lungs and other tissues.[56] The extracellular domain of ACE2 is cleaved from the transmembrane domain by another enzyme known as sheddase, and the resulting soluble protein is released into the blood stream and ultimately excreted into urine.[57][58]

Coronavirus entry point:
As a transmembrane protein, ACE2 serves as the main entry point into cells for some coronaviruses, including HCoV-NL63,[47] SARS-CoV, the virus that causes SARS,[59][60][61] and SARS-CoV-2,[62] the virus that causes COVID-19.[63][64][65][66]

This might lead some to believe that decreasing the levels of ACE2, in cells, might help in fighting the infection. On the other hand, ACE2 has been shown to have a protective effect against virus-induced lung injury by increasing the production of the vasodilator angiotensin 1–7.[67][non-primary source needed]

Furthermore, according to studies conducted on mice, the interaction of the spike protein of the coronavirus with ACE2 induces a drop in the levels of ACE2 in cells through internalization and degradation of the protein and hence may contribute to lung damage.[61][68][69]

Both ACE inhibitors and angiotensin receptor blockers (ARBs) that are used to treat high blood pressure have been shown in rodent studies to upregulate ACE2 expression hence may affect the severity of coronavirus infections.[70][71] However, multiple regulatory bodies have recommended continuing standard ACE inhibitor and ARB therapy.[72]

ACE Inhibitor:
Angiotensin-converting-enzyme inhibitors (ACE inhibitors) are a class of medication used primarily for the treatment of high blood pressure and heart failure.[73][74] They work by causing relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart. They work by causing relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart.

ACE inhibitors inhibit the activity of angiotensin-converting enzyme, an important component of the renin–angiotensin system liable to convert angiotensin I to angiotensin II,[75] and hydrolyse bradykinin[73] Thereby, ACE inhibitors in turn decrease the formation of angiotensin II, a vasopressin, but increase the level of bradykinin, a peptide vasodilator.[75][73]This combination, thereby, is synergistic in increasing ACE inhibitors' blood pressure-lowering effect.[75][73]Frequently prescribed ACE inhibitors include benazepril, zofenopril, perindopril, trandolapril, capt opril, enalapril, lisinopril, and ramipril.

Angiotension II receptor blocker:
Angiotensin II receptor blockers (ARBs), also known as angiotensin receptor blocker,[76][77] angiotensin II receptor antagonists, or AT_1 receptor antagonists, are a group of pharmaceuticals that bind to and inhibit the angiotensin II type 1 receptor (AT1) and thereby block the arteriolar contraction and sodium retention effects of renin–angiotensin system.[78]

Their main uses are in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure. They selectively block the activation of AT_1 receptors, preventing the binding of angiotensin II compared to ACE inhibitors.[78]

Other therapies:
Among other therapeutic strategies, systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended. Moreover, unselective or inappropriate administration of antibiotics should be avoided, although some centers recommend it. Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used. Multiple studies globally are investigating the use of remdesivir, a broad-spectrum antiviral.

2. Conclusion

Above article is totally based upon current findings on coronavirus. So here some conclusion points which might be helpful to produce novel drug.

Corona viruses are large pleomorphic spherical particles with bulbous surface projections.

A subset of corona viruses (specifically the members of betacoronavirus subgroup A) also have a shorter spike-like surface protein called hemagglutinin esterase (HE).

Hemagglutinin esterase (HEs) is a glycoprotein that certain enveloped viruses possess and use as invading mechanism. HEs helps in the attachment and destruction of certain sialic acid receptors that are found on the host cell surface.

Coronavirus get attached with human cell and invaded into it.

To avoid we can block attachment of virus to human cell by blocking receptor site located in human cell. In other work we can also degrade virus's spike like surface protein by some targeted molecule.

Furthermore still lots of research works going on this pendemic crises, hopefully soon we will get novel drug to attack coronavirus.

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