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COVID 19- HUMAN CORONA VIRUSE

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ABSTRACT

Human corona viruses (HCoVs) are known respiratory pathogens associated with a range of respiratory outcomes. In the past 12- 14 years, the onset of severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS-CoV) have thrust HCoVs into spotlight of the research community due to their high pathogen city in humans. Corona viruses possess a distinctive morphology, the name being derived from the outer fringe, or "Corona" of embedded envelope protein. Members of the family *corona viridae* cause a broad spectrum of animal and human diseases. Uniquely, replication of the RNA genome proceeds through the generation of a nested set of viral mRNA molecules. The study of HCoV-host interaction has contributed extensively to our understanding of HCoV pathogenesis. In present time, the pandemic of corona virus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. No proven effective therapies for this virus currently exist. The rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The most promising therapy is remdesivir. Remdesivir has potent in vitro activity against SARS-CoV-2, but it is not US Food and Drug Administration approved and currently is being tested in ongoing randomized trials.

KEYWORDS: Human corona virus, Respiratory Pathogens, Genome, Unprecedented, Pandemic.

INTRODUCTION

Human corona viruses (HCoVs) represent a major group of corona viruses (CoVs) associated with multiple respiratory diseases of varying severity, including common cold, pneumonia and bronchiolitis.[1] Today, HCoVs are recognized as one of the most rapidly evolving viruses owing to its high genomic nucleotide substitution rates and recombination.[2] In recent years, evolution of HCoVs has also been expedited by factors such as urbanization and poultry farming. These have permitted the frequent mixing of species and facilitated the crossing of species barrier and genomic recombination of these viruses.[3] To date, six known HCoVs have been identified, namely HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS-CoV); of which, four HCoVs (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) are globally circulated in the human population and contribute to approximately one-third of common cold infections in humans.[4] In severe cases, these four HCoVs can cause life-threatening pneumonia and bronchiolitis especially in elderly, children and immune compromised patients.[1,5,6] Besides respiratory illnesses, they may also cause enteric and neurological diseases.[7,8,9,10,11]

History

Corona virus disease was first described in 1931, with the first corona virus (HCoV-229E) isolated from humans in 1965. Until the outbreak of severe acute respiratory syndrome in late 2002, only two human corona viruses (HCoVs) were known – HCoV-229E and HCoV-OC43. Once the SARS corona virus (SARS-CoV) had been identified, two further human corona viruses were identified. Three groups of corona viruses exist: group 1 (HCoV-229E and HCoV-NL63), group 2 (HCoVOC43 and HCoV-HKU1), group 3 (no human CoVs as yet). SARS-CoV is an outlier to all three groups, although some place it in group 2.[12]

Classification

Order: Nidovirales	
Family: Corona viridae	
Genus	**Species**
Corona virus	Human corona virus 229E Human corona virus OC43 Human corona virus NL63 Human corona virus HKU1 Severe acute respiratory syndrome corona virus Human enteric corona virus
Toro virus	Human toro virus

Structure

Positive sense single stranded RNA
Genome ~30 000 nucleotides long
Pleomorphic viruses
80 × 160 nm diameter, with 12–24 nm surface projections (spikes) that cause the corona (Latin: crown) appearance
Major proteins:
S – Spike
E – Envelope
M – Membrane
N – Nucleocapsid

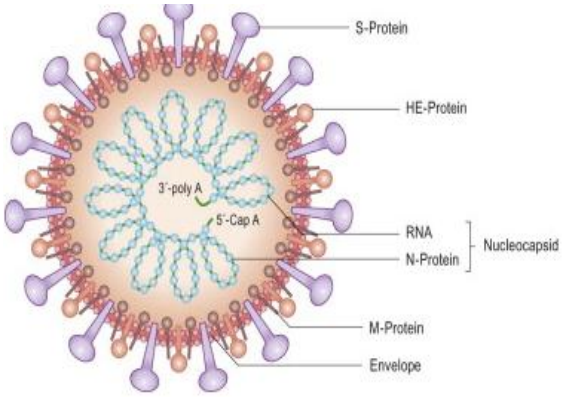

Figure 1: Corona virus.[12]

Involvement of Host Factors in Viral Replication and Pathogenesis

As intracellular obligate parasites, HCoVs exploit the host cell machinery for their own replication and spread. Since virus–host interactions form the basis of diseases, knowledge about their interplay is of great research interest. Here, we describe what is currently known of the cell's contribution in CoV infection cycle: attachment; entry into the host cell; translation of the replicase-transcriptase; replication of genome and transcription of mRNAs; and assembly and budding of newly packaged virions (figure 2).[13]

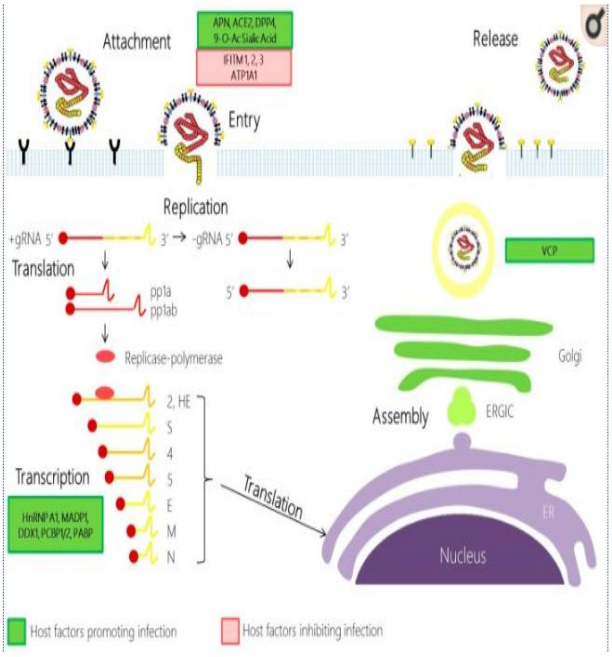

Figure 2: Corona virus replication cycle. Corona virus infection begins with the attachment of the S1 domain of the spike protein (S) with its cognate receptor. This drives the conformational change in the S2 subunit in S, promoting the fusion of the viral and cell plasma membrane. Following the release of the nucleocapsid to the cytoplasm, the viral gRNA is translated through ribosomal frame shifting to produce polyproteins pp1a and pp1ab. pp1a and pp1ab are auto proteolytically processed by host and viral proteases to generate 16 non-structural proteins (NSPs), which will then be assembled to form the replicase-polymerase. The replicase-polymerase is involved in the corona viral replication, a process in which the genomic RNA is replicated and the sub genomic RNA will be transcribed and translated to form the structural proteins. The viral products produced will be assembled in the ERGIC, and bud out as a smooth-wall vesicle to the plasma membrane to egress via exocytosis. Host factors that promote infection and inhibit infection are highlighted in green and red, respectively. APN, amino peptidase N; ACE2, Angiotensin converting enzyme 2; DPP4, dipeptidyl peptidase 4; 9-O-Ac Sialic Acid, 9-O-Acetylated Sialic Acid; IFITM, Interferon induced transmembrane protein;

ATP1A1, ATPase, Na+/K+ Transporting, Alpha 1 Polypeptide; HnRNP A1, Heterogeneous nuclear ribonucleoprotein A1; MADP1, Zinc Finger CCHC-Type and RNA Binding Motif 1; DDX1, ATP-dependent RNA Helicase; PCBP1/2, Poly r(C) binding protein 1/2; PABP, Poly A binding protein; COPB2, Coatomer protein complex, subunit beta 2 (beta prime); GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; ERGIC, Endoplasmic reticulum Golgi intermediate compartment; ER, endoplasmic reticulum; VCP, Valosin-Containing Protein.[13]

Attachment and entry of corona virus in host cell

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein.[14] Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles.[15-17] These viral lifecycle steps provide potential targets for drug therapy (Figure3). Promising drug targets include nonstructural proteins (eg, 3-chymotrypsin-like protease, papain like protease, RNA-dependent RNA polymerase), which share homology with other novel corona viruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways.[18,19]

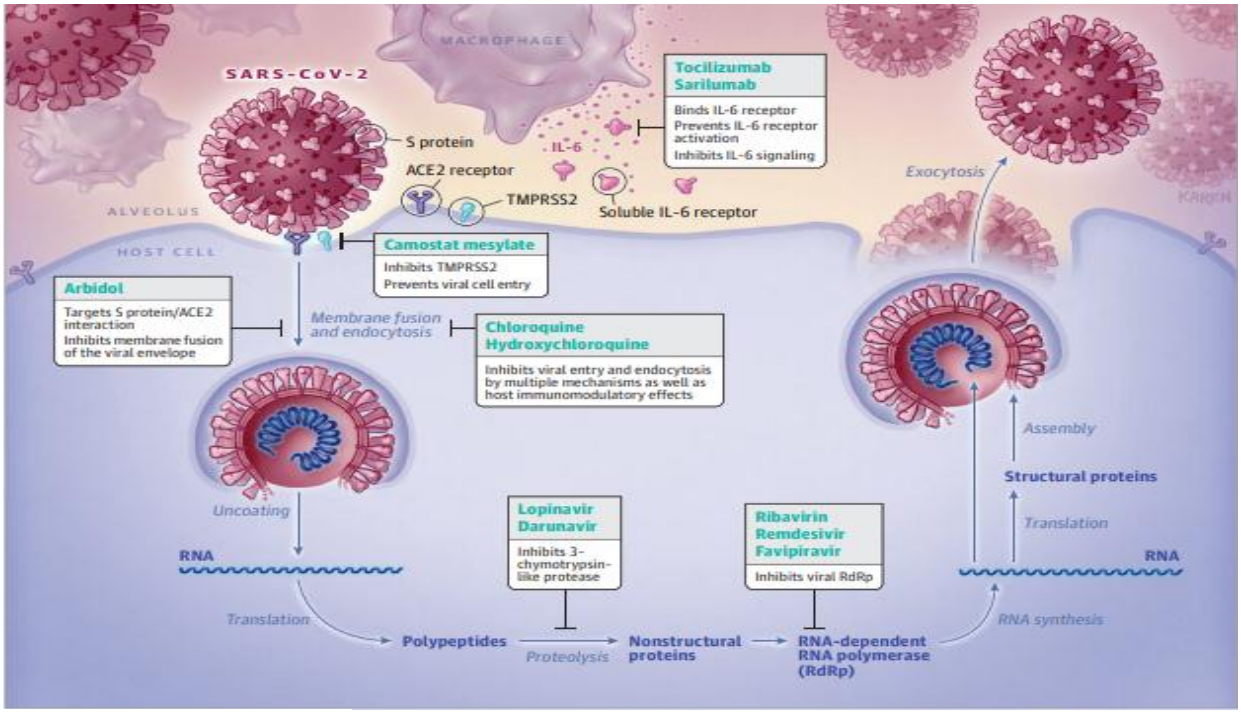

Figure 3: schematic represents of virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

Replication of corona virus

Succeeding the release and uncoating of viral nucleocapsid to the cytoplasm, CoV replication begins with the translation of ORF 1a and 1b into polyproteins pp1a (4382 amino acids) and pp1ab (7073 amino acids). Here, the downstream ORF1b is translated through ribosomal frame shifting mechanism, in which a translating ribosome shifts one nucleotide in the _1 direction, from the ORF1a reading frame into ORF1b reading frame. This repositioning is enabled by two RNA elements—a 51-UUUAAAC-31 heptanucleotide slippery sequence and RNA pseudoknot structure. Subsequently, polyproteins pp1a and pp1ab are cleaved into at least 15 nsp, which assemble and form the replication-transcription complex. With the assembly of the replicase-polymerase, the full-length positive strand of genomic RNA is transcribed to form a full-length negative-strand template for the synthesis of new genomic RNAs and overlapping subgenomic negative-strand templates. These subgenomic mRNAs are then transcribed and translated to produce the structural and accessory proteins. Several heterologous nuclear ribonucleoprotein (hnRNA) family members (hnRNPA1, PTB, SYN-CRYP) have been found to be essential for efficient RNA replication.[20] Other RNA-binding proteins have also been suggested to play a role in CoV replication, such as m-aconitase and poly-A-binding protein (PABP), DDX1, PCBP1/2 and zinc finger CCHC-type and RNA-binding motif 1 (MADP1).[21-23]

Assembly and departure of corona virus

The assembly of virions is quickly ensued with the accumulation of new genomic RNA and structural components. In this phase of the infection cycle, the helical nucleocapsid containing the genomic RNA interacts with other viral structural proteins (S, E andMproteins) to form the assembled virion. The assembly of CoV particles is completed through budding of the helical nucleocapsid through membranes early in the secretory pathway from the endoplasmic reticulum to the Golgi intermediate compartment (ERGIC). The contributions of the host in this phase of the infection cycle have rarely been explored. Currently, it is known that the M protein orchestrates the entire assembly process by selecting and organizing the viral envelope components at the assembly sites and by mediating the interactions with the nucleocapsid to allow the budding of virions.[24] The M protein interacts with different viral structural proteins, such as the E protein, to assemble into a mature virus. This interaction generates the scaffold of the virion envelope and induces the budding and release of the M protein-modified membrane and with the S protein to assemble the spikes into the viral envelope.[24,25] Following assembly and budding, the virions are transported in vesicles and eventually released by exocytosis. In a recent study, an inhibition of a Valosin-containing protein (VCP/p97) resulted in virus accumulation in early endosome in infectious bronchitis virus (IBV), suggesting a role for VCP in the maturation of virus-loaded endosomes.[26]

Clinical symptoms

Corona viruses are an important cause of the common cold – 2–10%, second after rhinoviruses. The common clinical features include

- Fever (not in all)
- Cough
- Sore throat
- Headache
- Fatigue
- Headache
- Myalgia and
- Breathlessness

Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα.[27] The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8d. The need for intensive care admission was in 25–30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd week. The median duration of hospital stay in those who recovered was 10 d. adverse outcomes and death is more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3%.[28]

Diagnosis

Due to the mild and passing nature of the illness, diagnosis is seldom required and is usually limited to diagnosis in the recovery period or of past infections in epidemiological studies. Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood. It must be remembered that the multiplex PCR panels currently available do not include the COVID-19. Commercial tests are also not available at present. In a suspect case in India, the appropriate sample has to be sent to designated reference labs in India or the National Institute of Virology in Pune. As the epidemic progresses, commercial tests will become available. Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimmer, CPK and LDH may be elevated and high levels are associated with severe disease. The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The CT is more sensitive and specific. CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing.[29]

Treatment

There is no specific treatment for corona viruses. Treatment is symptomatic and supportive. The first step is to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers. Supportive treatment, such as ventilation, was the centerpiece of the management of a SARS patient. Specific treatments, such as steroids, remain controversial regarding their effect, whether adverse or beneficial, on SARS patients. Mild symptoms of illness should be managed at home. Customary use of antibiotics and antiviral such as oseltamivir should be avoided in confirmed cases.[30] In oxygen deficient patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated.[31]

Supportive treatment, such as ventilation, was the centerpiece of the management of a SARS patient. Specific treatments, such as steroids, remain controversial regarding their effect, whether adverse or beneficial, on SARS patients. Ribavirin was used, as it is a broad-spectrum guanosine analogue, and appeared to have some benefit, as did other agents that have an effect on the inflammatory response, such as chloroquine and interferon, and agents that interfere with corona virus protease activity, such as the lopinavir/ritonavir combination used for HIV treatment. SARS-specific immunoglobulin was also tried. The degree to which any of these was successful as treatment is still debated. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS.[32,33] Detailed guidelines for critical care management for COVID-19 have been published by the WHO.[34] In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone.[27]

There is unreliable experience with use of remdesivir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19.[35] More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferon, chloroquine and plasma of patients recovered from COVID-19.[30,36,37] Chloroquine increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV and thereby it has the potential to block viral infection.[38] In addition, chloroquine also inhibits the quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins required for ligand recognition) that makes this agent a broad antiviral agent. From previous experimental studies have also demonstrated that chloroquine has potent anti-SARS-CoV-1 effects in vitro, primarily ascribable to a deficit in the glycosylation receptors at the virus cell surface, so that it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine. Since SARS-CoV-2 utilizes the similar surface receptor ACE2, it is consider that chloroquine can also interfere with ACE2 receptor glycosylation thus prevents SARS-CoV-2 attachment to the target cells.[38-41] Nevertheless, based on limited available evidences to date, and given the prevailing pandemic of COVID-19, some of the institutions and or organizations have already recognized the utility of chloroquine and HCQ.[42] A Central Clinical Task Force from Korea who have treated 27 cases of COVID-19 recommend using lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxychloroquine 400 mg orally per day for 7-10 days, in moderate to severe case of COVID-19.[43]

CONCLUSION

Future research on coronaviruses will continue to investigate many aspects of viral replication and pathogenesis. First, understanding the propensity of these viruses to jump between species, to establish infection in a new host, and to identify significant reservoirs of coronaviruses will dramatically aid in our ability to predict when and where potential epidemics may occur.

Although evidence of chloroquine and HCQ is limited (based on the experimental data and only two small human trials), considering the potentially favorable benefit-risk balance of chloroquine and HCQ in absence of any other valid treatment option, we believe that such treatment could be useful in the current context of pandemic COVID-19 outbreak.

Declaration of competing interest

We hereby declare that we have no conflict of interest related to this article.

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