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CORONA VIRUS COVID-19, HUMAN CORONAVIRUSES A REVIEW OF VIRUS

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ABSTRACT

The Novel Coronavirus (2019-nCoV) outbreak has been traced in China late 2019 and then was transmitted into more than 25 countries. A total 59 papers have been published in 20 journals during last January to March. Human coronaviruses (HCoVs) are known respiratory pathogens associated with a range of respiratory outcomes. In the past 14 years, the onset of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have thrust HCoVs into spotlight of the research community due to their high pathogenicity in humans. The study of HCoV-host interactions has contributed extensively to our understanding of HCoV pathogenesis. In this review, we discuss some of the recent findings of host cell factors that might be exploited by HCoVs to facilitate their own replication cycle. We also discuss various cellular processes, such as apoptosis, innate immunity, ER stress response, mitogen-activated protein kinase (MAPK) pathway and nuclear factor kappa B (NF-κB) pathway that may be modulated by HCoV.

KEYWORDS: Corona, virus, HCoV, pathogen.

INTRODUCTION

Human coronaviruses (HCoVs) represent a major group of coronaviruses (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 coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (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 immunocompromised patients.[1,5,6] Besides respiratory illnesses, they may also cause enteric and neurological diseases.[7–11]

Table 1: Classification of human coronavirus.

Coronaviriniae Genera Strains	**Discovery**	**Cellular Receptor**	**Host**
Alpha-coronavirus HCoV-229E	1966	Human Aminopeptidase N (CD13)	Bats
HCoV-NL63	2004	ACE2	Palm Civets, Bats
HCoV-OC43	1967	9-*O*-Acetylated sialic acid	Cattle
Beta-coronavirus HcoV-HKU1	2005	9-*O*-Acetylated sialic acid	Mice
SARS-CoV	2003	ACE2	Palm Civets, Bats
MERS-CoV	2012	DPP4	Bats, Camels

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).

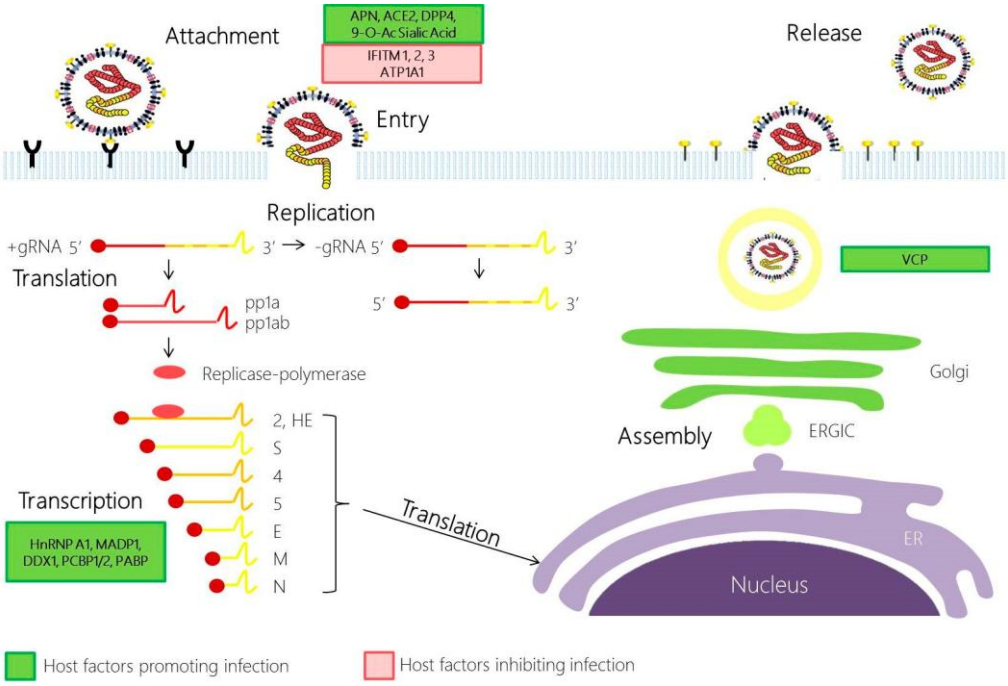

Figure 2: Coronavirus replication cycle. Coronavirus infection begins with the attachment of the S1 domain of the spike protein (S) with its cognate receptor. This drives the conformational change in the S2 subunit in S, promoting the fusion of the viral and cell plasma membrane. Following the release of the nucleocapsid to the cytoplasm, the viral gRNA is translated through ribosomal frameshifting to produce polyproteins pp1a and pp1ab. pp1a and pp1ab are autoproteolytically 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 coronaviral replication, a process in which the genomic RNA are replicated and the subgenomic 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, aminopeptidase 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.

Coronavirus Attachment and Entry

CoV infection is initiated by the attachment to specific host cellular receptors via the spike (S) protein. The host receptor is a major determinant of pathogenicity, tissue tropism and host range of the virus. The S protein comprises of two domains: S1 and S2. The interaction between the S1 domain and its cognate receptor triggers a conformational change in the S protein, which then promotes membrane fusion between the viral and cell membrane through the S2 domain. Today, the main host cell receptors utilised by all HCoVs are known: aminopeptidase N by HCoV-229E[26], angiotensin-converting enzyme 2 (ACE2) by SARS-CoV[27] and HCoV-NL63[28,29], dipeptidyl peptidase 4 (DPP4) by MERS-CoV.[30] and 9-*O*-acetylated sialic acid by HCoV-OC43 and HCoV-HKU1.[31,32]

Apart from the conventional endosomal route of entry, some CoVs may also gain entry into the cell via the non-endosomal pathway, or a combination of both. The low pH in the cellular environment and endosomal cysteine protease cathepsins may help to facilitate membrane fusion and endosomal CoV cell entry.[33] Recent evidence has supported the role of cathepsin L in SARS-CoV and MERS-CoV entr.[34–36] Other host proteases, such as transmembrane protease serine 2 (TMPRSS2) and airway trypsin-like protease TMPRSS11D, could also perform S1/S2 cleavage to activate the S protein for non-endosomal virus entry at the cell plasma membrane during HCoV-229E and SARS-CoV infection.[37,38] In addition, MERS-CoV is also activated by furin, a serine endopeptidase that has been implicated in the cell entry of other RNA viruses and S1/S2 cleavage during viral egress.[39]

Many host cells also utilise its own factors to restrict viral entry. Using cell culture system and pseudotype virus, many groups have identified a family of interferon inducible transmembrane proteins (IFITM), which could inhibit global circulating HCoV-229E and HCoV-NL63 S protein mediated entry, and also the highly pathogenic SARS-CoV and MERS-CoV.[12,40] While the IFITM mode of action remains elusive, cell-to-cell fusion assays performed by some research groups suggest that IFITM3 blocks the enveloped virus entry by preventing fusion of the viral envelope with the plasma membrane or endosomal membranes through modulating the host membrane fluidity.[41]

Sources of 2019-nCoV outbreak

For the first time, the researchers have correlated the 2019-nCoV infection with the Huanan South China Seafood Market (HSCM) since the first cases were associated with this marker.[12] However, the first case recorded outside China for a Chinese tourist in Thailand

has no epidemiological linkage to the HSCM.[13] The studies which indicated to the HSCM as a potential source for 2019-nCoV depended on that the HSCM have several types of wild animals such as snakes, birds, marmots and bats which are the natural reservoir for the virus. Moreover, according to WHO, all environmental samples from HSCM was positive for 2019-nCoV. However, there was no specific animal association identified.[14] The genome sequencing for the 2019-nCoV claimed that the snake is the wildlife reservoir. The theory depend on the principle of origin-unknown homologous recombination which was identified within the spike glycoprotein of the 2019-nCoV and might be used for explaining the snake-to-human cross- species transmission. Other authors believed that the bats is the natural reservoir.[15]

Pathogenicity and Symptoms

The incubation period of 2019-nCoV is between 7 and 14 days.[16] The fever is the most frequently symptoms, followed by malaise, dry cough, respiratory distress and shortness of breath.[13] The disease is also associated with, acute respiratory distress syndrome requiring intensive care, acute cardiac injury, diarrhoea, renal function tests, deranged liver, multiorgan dysfunction syndrome, and lymphopenia, septic shock and multi-organ failure. The mortality has been estimated to be between 10 and 30% compared to SARS-CoV (10% mortality) and MERS- CoV (35% mortality).[12] Chen et al.[17] investigated 99 patient with 2019-nCoV infections. The results revealed that more than the age of the patient ranged from 40 to 70 years old, 50% of them have no direct relation to HSCM. RT-PCR was effective in detected 51% of the infections. The most common symptoms were fever, cough, muscle ache, confusion, headache, sore throat, rhinorrhea, chest pain, shortness of breath, diarrhea, and nausea and vomiting. The imaging examination revealed presence of bilateral pneumonia, multiple mottling and ground-glass opacity, and pneumothorax. The 2019-nCoV associated with acute respiratory distress syndrome and multiple organ failure.

Transmission route

Up to mid of January there was no clear evidence of human to human transmission.[13] However, currently, one of the main serious problem with 2019-nCoV is the transmission route, since its can easily transmitted through the daily practices such as shaking hands, touching contaminated objects, or kissing. The studies have detected the virus in the patient stool which does mean that the virus has the potential transmission through the faecal–oral route.[9] Besides, it can survive for long time in the environment. However, it has to mention

that the virus could be transmitted through the respiratory droplets not the air.[18] For this reason the musk is effective to present the transmission of virus from the patient to the others while the musk itself could not prevent the infection. The second main concern with the virus transmission is the rapid of the transmission it has mentioned that one patient can transmit the virus to 14 around people. In a comparison to SARS- and MERS-CoV outbreak which has associated with super spreading (R0>10), based on the data published up to 21 January, the 2019-nCoV has low R0.[12] However, at the moment the high increasing in the infected cases indicated that the virus has a super-spreading individuals fueling the outbreak. The most susceptible populations included whom who have significant health conditions such as diabetes, hypertension and heart and/or kidney function issues. In comparison during the MERS-CoV outbreak most Susceptible Populations were the smokers and whom have a cardiovascular disease, diabetes, hypertension and other chronic illnesses.[19]

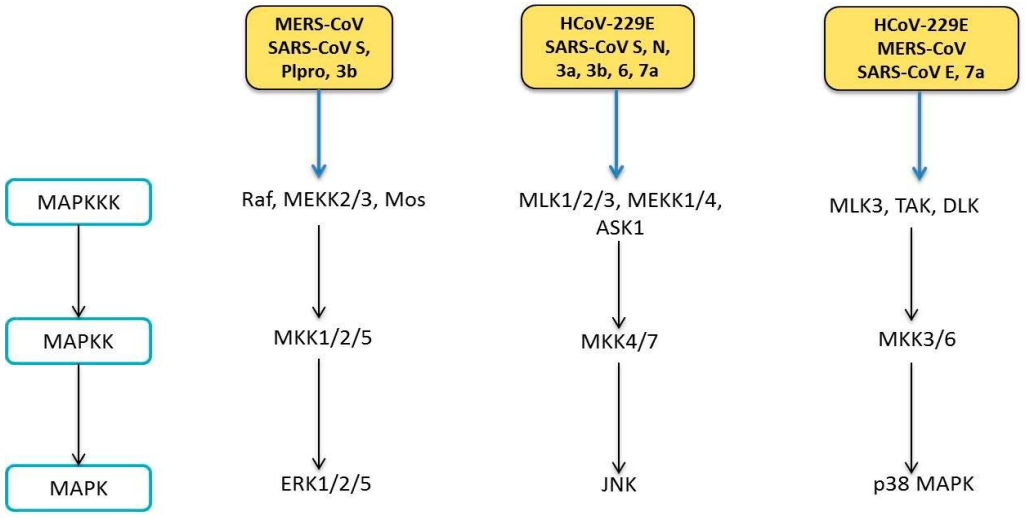

Figure 1: HCoVs on MAPK signalling pathways. MAPK pathways comprises of the ERK, JNK and p38 MAPK pathways. During HCoV infections, the signals are transduced by the MAPK pathways by a three-tier protein kinase cascade, with the kinase of each tier being phosphorylated by upstream kinases at the Thr and Tyr residues. HCoVs and their viral proteins (yellow-orange boxes) have been shown to induce these MAPK pathways as shown in the figure.

Diagnostic

Since the 2019-nCoV outbreak, the diagnostic methods of the virus in human clinical specimens included, real-time RT-PCR, next-generation sequencing, Scanning electron microscopy (SEM) and cell culture.[7,20] In contrast, commercially available multiplex NAAT tests were ineffective for diagnostic the patient with 2019-nCoV.[21] This can explain the

delay preventing the 2019-nCoV outbreak since the cell culture, PCR and SEM need a period to detect the virus in the samples. The CT findings included consolidative pulmonary opacities and bilateral pulmonary parenchymal ground-glass. In sometimes the symptoms associated with a rounded morphology and a peripheral lung distribution.[22] The chest radiograph for a patient after 8 days of the diseases showed bilateral lung consolidation with relative peripheral sparing while was more extensive after 11 days. However, the bilateral ground-glass opacity is among the most common in the 2019-nCoV patients.[23]

Genome organization and therapeutics

Different studies have recorded different findings, for instance Chan et al.[3] revealed that 2019- nCoV similar to bat SARS-like-CoVZXC21 by 89%, while similar human SARS-CoV by 82%. Paraskevis et al.[24] suggested that the 2019-nCoV is very close to BatCoV RaTG13 by 96.3%. However, there is a discordant clustering with the Bat_SARS-like coronavirus sequences. These findings also indicated that the current 2019-nCoV is neither a mutated strain for SARS nor as a result of a recent recombination event. Zhu et al.[20] revealed that the full genome sequence analysis of 2019-nCoV indicate that the current virus is belongs to revealed that belongs to beta corona virus. However, no similarity was recorded in comparison to MERS-CoV and SARS- CoV. Gralinski and Menachery[12] mentioned that 2019-nCoV spike protein has roughly 75% amino acid identity with SARS-CoV. Lu et al.[25] revealed that 2019-nCoV is very close to severe acute respiratory syndrome (SARS) by 88% while was similar to SARS-CoV by 79% and MERS-CoV by 50%. Up to date no effective medicine is effective against 2019-nCoV, some of authors have suggested to use HIV medicine to enhance the immune system while others suggested to use Baricitinib as potential treatment for 2019-nCoV acute respiratory disease.[11] However, more investigation are require to finding an effective medicine and vaccines for coronavirus species to prevent occurrence of outbreak in future.

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