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HUMAN CORONAVIRUS: A REVIEW ON VIRUS CELL BIOLOGY AND INTERACTION TO HOST CELL

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ABSTRACT

Corona viruses are enveloped positive-stranded RNA and are characterized by club-like spikes that project from their surface, a remarkably large RNA genome, and a unique replications style in the cytoplasm. Deliver their nucleocapsid into the host cell, they depend on the fusion of their envelope with the host cell membrane. The spike glycoprotein mediates virus entry and is a prime determinant of cell tropism and pathogenic. In most, corona viruses, S is slashed by a host cell spring-like protease into two separate polypeptides noted S1 and S2. S1 facilitates virus infection by binding to host receptors. It comprises two domains, the N-terminal domain and the C-terminal RBD domain that directly interacts with host receptors while S2 forms the stalk of the spike molecule which fuses the virus into host cell. After all its fusion, undergo replication/transcription of virion. It causes a variety of diseases in mammals and bird according to their classification. Here we provide a brief introduction of cell biology of corona viruses and host cell interaction process.

KEYWORD: corona virus; viral protein; viral entry; fusion and replication/transcription.

INTRODUCTION

Corona virus was first discovered in the 1930s which shows acute respiratory infection of domesticated chickens to be caused by infectious bronchitis virus (IBV). Later on, "Human corona virus," was invented in 1968. The name "coronavirus" is derived from Latin *corona*, meaning crown like morphology observed for these viruses in the electron microscope. In 1975, the *Coronaviridae* family was recognized by the International Committee on the Taxonomy of Viruses. Lately, at the 10th International *Nidovirus* Symposium in Colorado, Springs, Colo, in June 2005, it was projected that the *Coronaviridae* family be divided into two subfamilies, the corona viruses and the *toroviruses*, latter of which cause enteric diseases in cattle and possibly in humans. The *Coronaviridae* family, along with the *Arteviridae*, *Mesoniviridae* and *Roniviridae* families, form the *Nidovirales* order. The *Coronavirinae* are further subdivided into four genera, the alpha, beta, gamma, and delta corona viruses (*see* Table1 list of viruses). All viruses in the *Nidovirales* order are enveloped, non-demented positive-sense RNA viruses. They all contain very large genomes for RNA viruses, with some viruses having the largest identified RNA genomes, containing up to 33.5 Kb genome.[1]

Table 1: Coronavirus genera, species and interacting receptors.

Genus	Species	Receptor
Alphacoronavirus	• Alphacoronavirus 1 comprising: ○ Feline Coronavirus (FCoV) serotype 2 ○ Canine Coronavirus (CCoV) serotype2 ○ Transmissible gastroenteritis virus (TGEV) • Human coronavirus 229E • Human coronavirus NL63 • Porcine Epidemic Diarrhea Coronavirus (PEDV) • Rhinolophus bat coronavirus HKU2 • Scotophilus bat coronavirus 512/05 • Miniopterus bat coronavirus 1 • Miniopterus bat coronavirus HKU8	 Aminopeptidase N Aminopeptidase N Aminopeptidase N Aminopeptidase N ACE2 Aminopeptidase N
Beta coronavirus	• Beta coronavirus 1 comprising: ○ Bovine coronavirus (BCoV) ○ Human coronavirus OC43(HCoV-OC43) ○ Equine coronavirus (ECoV) ○ Human enteric coronavirus (HECoV) ○ Porcine hemagglutinating encephalomyelitis virus (PHEV) ○ Canine respiratory coronavirus (CrCoV) • Murine coronavirus comprising: ○ Existing species of mouse hepatitis virus (MHV) ○ Rat coronavirus ○ Puffinosis virus • Human coronavirus HKU9 • Rousettus bat coronavirus HKU4 • Tylonycteris bat coronavirus HKU5 • SARSr-CoV (SARS related Coronavirus) comprising ○ Human SARS-CoV ○ Rhinolophus bat viruses	 Neu 5,9 Ac2 Neu 5,9 Ac2 CEACAM1 ACE2
Gamma coronavirus	• Avian coronavirus comprising: ○ IBV ○ Various coronaviruses infecting turkey, pheasant, duck, goose and pigeon • Beluga Whale coronavirus SW1	
Delta coronavirus	• Bulbul coronavirus HKU11 • Thrush coronavirus HKU12 • Munia coronavirus HKU13	

Corona viruses are enveloped, spherical or pleiomorphic viruses, with typical sizes starting from 80 to 120 nm. (Fig.1) They have a 5' capped, single-strand positive sense RNA genome with a length between 21.3 kb, the longest amongst all RNA viruses. The genome is self-possessed of six to ten open reading frames (ORFs). The primary ORF includes two-thirds of the genome and encodes the replicase proteins, where the last third contains the structural protein genes in a very fixed order: S-E-M-N Variable numbers of ORF encoding accessory proteins are present between these genes. The genome is packed into a helical nucleocapsid (N) surrounded by a host-derived lipid bilayer. The virion envelope contains a minimum of three viral proteins, the spike protein (S), the membrane protein (M) and therefore the envelope protein (E). Additionally, some coronaviruses also contain a hemagglutinin esterase (HE). Where the M and E proteins are intricate in virus assembly, the spike protein is that the leading intermediary of viral entry.[2] The S protein (~150 kDa), uses an N-terminal signal sequence to extend access to the ER, and is severely N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus. The trimeric S glycoprotein is a class I fusion protein and mediates attachment to the host receptor. In most, coronaviruses, S is slashed by a host cell furin-like protease into two separate polypeptides noted S1 and S2. S1 facilitates virus infection by binding to host receptors. It comprises two domains, the N-terminal domain and the C-terminal RBD domain that directly interacts with host receptors while S2 forms the stalk of the spike molecule.[3]

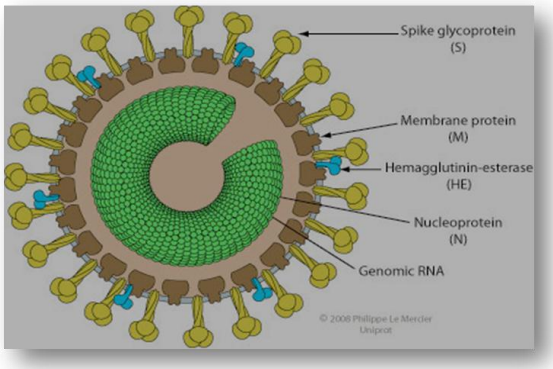

Fig. 1: Structure of virus.

1. Viral Protein:

1.1 Spike Protein (S): The coronavirus spike contains three segments: an oversized ectodomain, a single-pass transmembrane anchor, and a brief intracellular tail. The ectodomain consists of a receptor-binding subunit S1 and a membrane-fusion subunit S2. Microscopy studies discovered that the spike could be clove-shaped trimer with three S1 heads and a trimeric S2 stalk (Fig.2). During virus entry, S1 binds to a receptor on the host cell surface for viral attachment, and S2 fuses the host and viral membranes, allowing viral genomes to enter host cells. [4]

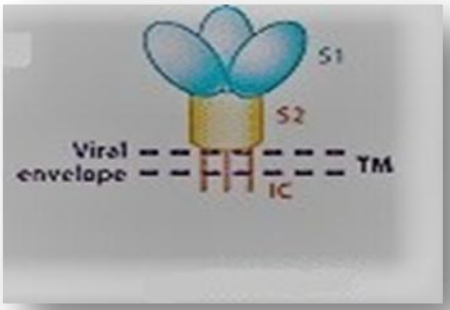

Fig. 2: Spike Protein.

1.2 Membrane Protein (M): Corona virus M proteins are divergent in their amino acid content, but all share the same overall the identical basic structural characteristics. They need three transmembrane domains, membrane (M) play key roles in virus assembly, through Membrane-Membrane (M-M), Membrane-spike (M-S), and Membrane-nucleocapsid (M-N) protein interactions, flanked by a brief amino-terminal glycosylated domain and an extended carboxyterminal tail located outside and inside the virion, respectively. M localizes within the Golgi region when expressed alone. M-M interactions constitute the general scaffold for the viral envelope. The S protein and a tiny low number of E molecules are interspersed within the M protein lattice in mature virions. Corona viruses assemble and bud at intracellular membranes within the region of the endoplasmic reticulum (ER) Golgi intermediate compartment (ERGIC). Co expression of only the M and therefore, the E proteins is sufficient for virus-like particle (VLP) assembly for many corona viruses.[5]

1.3 Envelope Protein (E): Corona virus envelope protein is a small membranes protein and minor component of the virus particles. It plays important roles in virion assembly and morphogenesis, alteration of the membrane permeability of host cells and virus-host cell interaction.[6] The E protein is a short, integral membrane protein of 76–109 amino acids, ranging from 8.4 to 12 kDa in size. The primary and secondary structure reveals that E has a short, hydrophilic amino terminus consisting of 7–12 amino acids, followed by a large hydrophobic transmembrane domain (TMD) of 25 amino acids, and ends with a long, hydrophilic carboxyl terminus, which comprises the majority of the proteins. The hydrophobic region of the TMD contains at least one predicted amphipathic α-helix that oligomerizes to form an ion-conductive pore in membranes.[7] E proteins all have large predicted hydrophobic domains, and it has been shown for MHV, IBV and SARS-CoV that E is integral membrane protein, although it does not contain a cleavable signal sequence.[8]

1.4 Nucleoprotein (N): Corona virus N proteins differ from 377 to 455 amino acids in length, a highly basic, and have a high (7 to 11%) serine content (i.e. nonessential amino acid derived from glycine), which are probable targets for phosphorylation.[9] Nucleoprotein proteins are phosphoproteins that are capable of binding to helix and have flexible structure of viral genomic RNA (30,000 nucleotide). It plays a very important role in virion structure, replication and transcription of corona viruses, because the N protein localizes in both the replication/ transcriptional region of the coronaviruses and the Endoplasmic Reticulum (ER) Golgi Intermediate Compartment (ERGIC) region where the virus is collected.[10]

2. Interaction of virus into the Host cell

2.1 Virus attachment and entry: CoV infection is started by the attachment to specific host cellular receptors through the spike (S) protein. The S protein divided into two domains. The amino-terminal S1 subunit contains the receptor-binding domain; while the carboxy-terminal S2 subunit contains domains required for fusion by endocytosis process. Receptor recognition by viruses is the first and essential step of viral infections of host cells. S1 contains two independent domains, N-terminal domain (S1-NTD) and a C-terminal domain (S1-CTD). The binding interaction between coronavirus receptor binding domain and its receptor is one of the most important determining factors of the coronavirus host range and cross-species infection. Today, the main host cell receptors utilised by all Human CoVs are known: aminopeptidase N by HCoV-229E, angiotensin-converting enzyme 2 (ACE2) by SARS-CoV and HCoV-NL63, dipeptidyl peptidase 4 (DPP4) by MERS-CoV, CEACAM-1 by MHV.[11,12,13]

In case of Mouse Hepatitis Virus replication process, the MHV virus binds to host cell receptor carcinoembryonic antigen-cell adhesion molecule called CEACAM-1 through interaction with spike glycoprotein. (fig) Prototype CEACAM1 or MHVR is composed of four Ig-like ectodomains (in the order N, A1, B, and A2 or D1, D2, D3, and D4 from the N terminus), a transmembrane domain (TM), and a cytoplasmic tail (Cy).[14]

2.2 Replication: After attachment of MHV virion to receptor it fuses positive-stranded genomic RNA (31.2kb) that are 5′ capped and 3′ polyadenylated into the host cell. The RNA-dependent RNA polymerase that mediates this infrequent, irregular RNA synthesis is

encoded by gene.[15] Some of gene gets transcriptase/replicase, in replicase process RNA dependent RNA polymerase enzyme form a (-) mRNA 3′ to 5′ sequence. For new virion progeny the replicate sequence again goes back to its original sequence i.e. 5′ to 3′.

2.3 Transcription: For MHV, gene composed of 22 kb and contains two large open reading frames ORF1a and ORF1b. which are translated as two polyprotein precursors, pp1a and pp1ab. The larger protein, pp1ab, is expressed by ribosomal frameshifting. [16] (Fig.3) During this process, mRNAs are generated that represent the genomic 5′ sequence, the so-called leader transcription-regulating sequence (TRS) merely plays a targeting role for strand transfer and 3′ sequence, called body transcription-regulating sequence (TRS) play a role of fulfils multiple functions. [17,18]

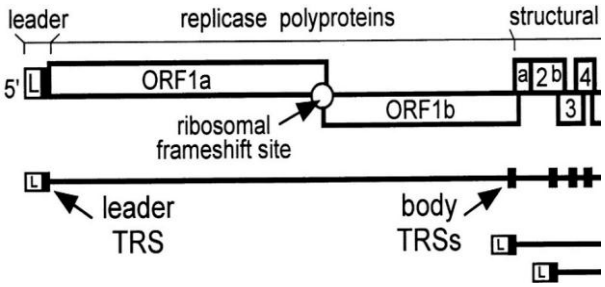

Fig. 3: Transcription of mRNA.

2.4 Virion assembly and Exocytosis: As per body TRS, structural gene sequence is responsible for formation of various protein for virus, and daughter cell get assemble in proper manner. This gene is further going to secretory pathway i.e. Rough Endoplasmic Reticulum (ER) - Golgi body (cisternae) – transport vesicle. After that a bulk of virion get release from host cell by exocytosis, and ready to infect another healthy host cell. In this way corona virus infect and spread host human cell.

CONCLUSION

From above study, we realize that the corona virus depends on spike protein for host cell interaction, large size and replication strategy of viral genome make their own daughter cell rapidly within few days and make infected other host cell. The implications of corona virus species barrier jumping are devastating and result in severe disease and mortality. And from daily updates we got realize that still we don't have any specific treatment for corona virus, so we have to require care, wash your hand with soap or use sanitisers. Please keep social distancing. Stay home and Stay safe.

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