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Coronavirus: an overview and details study about their replication & pathogenesis

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ABSTRACT

Coronaviruses (CoV) belong to the genus Corona virus with its high mutation rate in the Coronaviridae. Coronaviruses (CoVs), enveloped positive-sense RNA viruses, are characterized by club-like spikes that project from their surface, an unusually large RNA genome, and a unique replication strategy. Coronaviruses cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease chickens to potentially lethal human respiratory infections. Here we provide a brief introduction to coronaviruses discussing their replication and pathogenicity, and current prevention and treatment strategies. We will also discuss the outbreaks of the highly pathogenic Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV).as well as the medicines which are used for treatment of CoVs.

Keywords: *Corona, Covid-19, positive-sense RNA viruses; SARS-CoV; MERS-CoV, virology, pathogenesis*

Coronaviruses (CoV) belong to the genus Coronavirus in the Coronaviridae. All CoVs are pleomorphic RNA viruses characteristically containing crown-shape peplomers with 80-160 nM in size and 27-32 kb positive polarity.[1] Recombination rates of CoVs are very high because of constantly developing transcription errors and RNA Dependent RNA Polymerase (RdRP) jumps.[2] With its high mutation rate, Coronaviruses are zoonotic pathogens that are present in humans and various animals with a wide range of clinical features from asymptomatic course to requirement of hospitalization in the intensive care unit; causing infections in respiratory, gastrointestinal, hepatic and neurologic systems.[3]

Guangdong state of China for the first time in 2002 and 2003. Before these outbreaks, there were the two most known types of CoV as CoV OC43 and CoV 229E that have mostly caused mild infections in people with an adequate immune system.[3, 4] Approximately ten years after SARS

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this time, another highly pathogenic CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has emerged in the Middle East countries.[5] In December 2019, 2019 novel Coronavirus (nCoV), which is another public health problem, has emerged in the Huanan Seafood Market, where livestock animals are also traded, in Wuhan State of Hubei Province in China and has been the focus of global attention due to a pneumonia epidemic of unknown cause. [6].The novel SARS-CoV-2 coronavirus that emerged in the city of Wuhan, China, last year and has since caused a large scale COVID-19 epidemic and spread to more than 70 other countries is the product of natural evolution, according to findings published today in the journal *Nature Medicine*.[7]

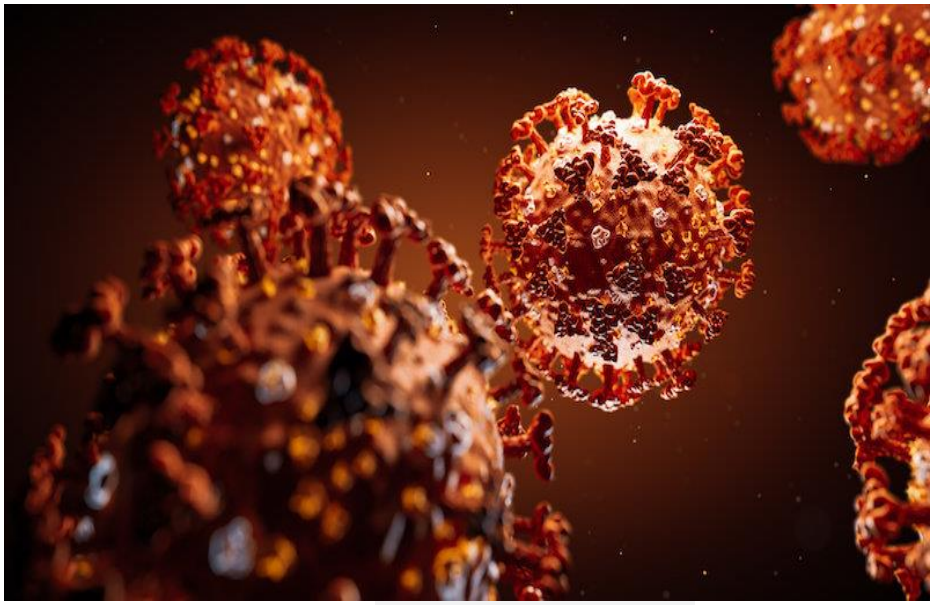


Fig. no.1- Coronavirus illustration

Epidemiology:- In December 2019, many pneumonia cases that were clus-tered in Wuhan city were reported and searches for the source have shown Huanan Seafood Market as the origin. The first case of the COVID-19 epidemic was discovered with unexplained pneumonia on December 12, 2019, and 27 viral pneumonia cases with seven being severe, were of-ficially announced on December 31, 2019.[7,9]

Classification:- Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, and Roniviridae families. The Coronavirinae comprise one of two subfamilies in the Coronaviridae family, with the other being the Torovirinae. The Coronavirinae are further subdivided into four groups, the alpha, beta, gamma and delta coronaviruses. The viruses were initially sorted into these groups based on serology but are now divided by phylogenetic clustering.

All viruses in the Nidovirales order are enveloped, non-segmented positive-sense RNA viruses. They all contain very large genomes for RNA viruses, with Coronavirinae having the largest identified RNA genomes, containing approximately 30 kilobase (kb) genomes. Other common features within the Nidovirales order include: i) a highly conserved genomic organization, with a large replicase gene preceding structural and accessory genes; ii) expression of many

nonstructural genes by ribosomal frameshifting; iii) several unique or unusual enzymatic activities encoded within the large replicase-transcriptase polyprotein; and iv) expression of downstream genes by synthesis of 3′ nested sub-genomic mRNAs. In fact, the Nidovirales order name is derived from these nested 3′ mRNAs as nido is Latin for "nest". The major differences within the Nidovirus families are in the number, type, and sizes of the structural proteins. These differences cause significant alterations in the structure and morphology of the nucleocapsids and virions.[10]

CORONAVIRUS LIFE CYCLE

Attachment and Entry- The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The sites of receptor binding domains (RBD) within the S1 region of a coronavirus S protein vary depending on the virus, with some having the RBD at the Nterminus of S1 (MHV) while others (SARS-CoV) have the RBD at the C-terminus of S1 [11,12]. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Many coronaviruses utilize peptidases as their cellular receptor. It is unclear why peptidases are used, as entry occurs even in the absence of the enzymatic domain of these proteins. Many αcoronaviruses utilize aminopeptidase N (APN) as their receptor, SARS-CoV and HCoVNL63 use angiotensin-converting enzyme 2 (ACE2) as their receptor, MHV enters through CEACAM1, and the recently identified MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) to gain entry into human cells.

Following receptor binding, the virus must next gain access to the host cell cytosol. This is generally accomplished by acid-dependent proteolytic cleavage of S protein by a cathepsin, TMPRRS2 or another protease, followed by fusion of the viral and cellular membranes. S protein cleavage occurs at two sites within the S2 portion of the protein, with the first cleavage important for separating the RBD and fusion domains of the S protein [13].

Replicase Protein Expression- The next step in the coronavirus lifecycle is the translation of the replicase gene from the virion genomic RNA. The replicase gene encodes two large ORFS, rep1a and rep1b, which express two co-terminal polyproteins, pp1a and pp1ab. In order to express both polyproteins, the virus utilizes a slippery sequence (5′-UUUAAAC-3′) and an RNA pseudoknot that cause ribosomal frameshifting from the rep1a reading frame into the rep1b ORF. In most cases, the ribosome unwinds the pseudoknot structure, and continues translation until it encounters the rep1a stop codon. Occasionally the pseudoknot blocks the ribosome from continuing elongation, causing it to pause on the slippery sequence, changing the reading frame by moving back one nucleotide, −1 frameshift, before the ribosome is able to melt the pseudoknot structure and extend translation into rep1b, resulting in the translation of pp1ab [14,15].

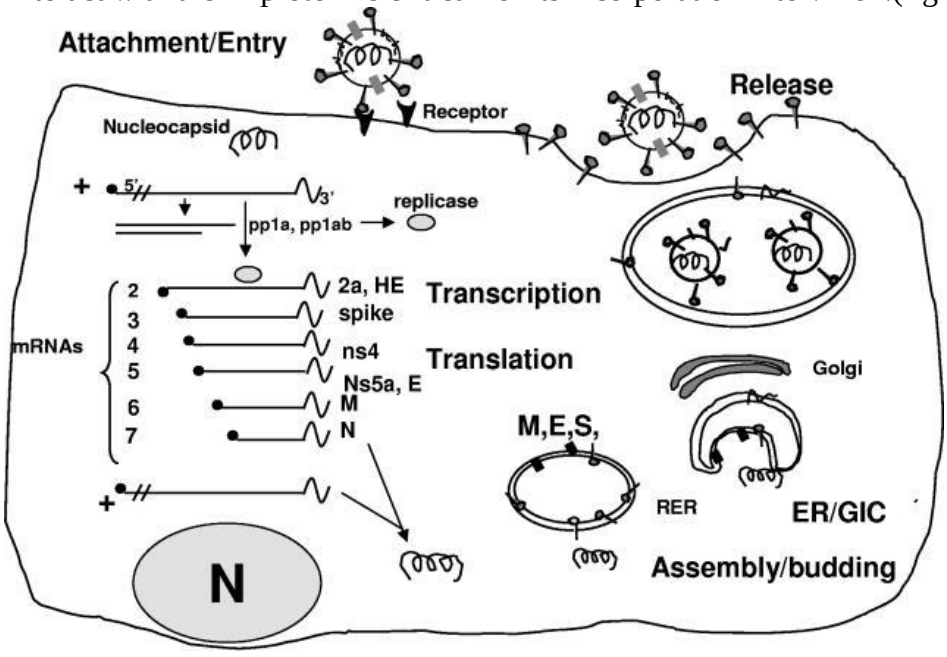
Polyproteins pp1a and pp1ab contain the nsps 1–11 and 1–16, respectively. In pp1ab, nsp11 from pp1a becomes nsp12 following extension of pp1a into pp1b. However γ-coronaviruses do not contain a comparable nsp1. These polyproteins are subsequently cleaved into the individual nsps [16]. Coronaviruses encode either two or three proteases that cleave the replicase polyproteins. They are the papain-like proteases (PLpro), encoded within nsp3, and a serine type protease, the main protease, or Mpro, encoded by nsp5. Most coronaviruses encode two PLpros within nsp3,

except the γ-coronaviruses, SARS-CoV and MERS-CoV, which only express one PLpro [17]. The PLpros cleave the nsp1/2, nsp2/3, and nsp3/4 boundaries while the Mpro is responsible for the remaining 11 cleavage events.

Replication and Transcription- Viral RNA synthesis follows the translation and assembly of the viral replicase complexes. Viral RNA synthesis produces both genomic and sub-genomic RNAs. Sub-genomic RNAs serve as mRNAs for the structural and accessory genes which reside downstream of the replicase polyproteins. All positive-sense sub-genomic RNAs are 3′ co-terminal with the full-length viral genome and thus form a set of nested RNAs, a distinctive property of the order Nidovirales. Both genomic and sub-genomic RNAs are produced through negativestrand intermediates. These negative-strand intermediates are only about 1% as abundant as their positive-sense counterparts and contain both poly-uridylate and anti-leader sequences [18].

Assembly and Release- Following replication and subgenomic RNA synthesis, the viral structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum (ER). These proteins move along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). There, viral genomes encapsidated by N protein bud into membranes of the ERGIC containing viral structural proteins, forming mature virions [19].

The M protein directs most protein-protein interactions required for assembly of coronaviruses. However, M protein is not sufficient for virion formation, as virus-like particles (VLPs) cannot be formed by M protein expression alone. However, when M protein is expressed along with E protein VLPs are formed, suggesting these two proteins function together to produce coronavirus envelopes [20]. N protein enhances VLP formation, suggesting that fusion of encapsidated genomes into the ERGIC enhances viral envelopment [21]. The S protein is incorporated into virions at this step, but is not required for assembly. The ability of the S protein to traffic to the ERGIC and interact with the M protein is critical for its incorporation into virion.(fig no.2)



Virology-Pathogenesis:- Coronaviruses are viruses whose genome structure is best known among all RNA viruses. Two-thirds of RNA they have encodes viral polymerase (RdRp), RNA synthesis materials, and two large nonstructural polyproteins that are not involved in host response modulation (ORF1a-ORF1b). The other one-third of the genome encodes four structural proteins (spike (S), envelope (E), membrane (M) ve nucleocapsid (N), and the other helper proteins.[22,23] Although the length of the CoV genome shows high variability for ORF1a/ORF1b and four structural proteins, it is mostly associated with the number and size of accessory proteins. [12,13] The first step in virus infection is the interaction of sensitive human cells with Spike Protein. Genome encoding occurs after entering to the cell and facilitates the expression of the genes, that encode useful accessory proteins, which advance the adaptation of CoVs to their human host. [23] Genome changes resulting from recombination, gene exchange, gene insertion, or deletion are frequent among CoVs, and this will take place in future outbreaks as in past epidemics. As a result of the studies, the CoV subfamily is rapidly expanding with new generation sequencing applications that improve the detection and definition of novel CoV species. In conclusion, CoV classification is continually changing. According to the most recent classification of The International Committee on Taxonomy of Viruses (ICTV), there are four genera of thirty-eight unique species.[24]

Sources & Modes of Transmission:- CoVs have been defined as a novel respiratory tract virus in the samples collected from the individuals who present symptoms of respiratory tract infection in 1962.[25] This is a large family of viruses that are common in many different animal species, including camels, cattle, cats, and bats. Rarely, animal CoVs can infect humans and, as a result, may spread among humans during epidemics such as MERS, SARS, and COVID-19.[26,27] At the onset of major outbreaks caused by CoVs, palm cats have been proposed to be a natural reservoir of Human CoVs for SARS and dromedary camels for MERS.[3] However, more advanced virological and genetic studies have shown that bats are reservoir hosts of both SARS-CoV and MERS-CoV and before these viruses spread to humans, they use the other responsible animals as intermediate hosts. Studies have reported that most of the bat CoVs are the gene source of alpha-CoV and beta-CoVs, while most of the bird CoVs are the gene source of gamma-CoVs and delta-CoVs.[3] In recent studies, it has been observed that the novel virus causing epidemics coincides with the CoV isolated in bats. Presence of wild animal trade in Huanan Seafoods Market where the first cases appeared, supports this finding.[28,29].

ROLES OF CORONAVIRUS PROTEINS IN PATHOGENESIS

Spike Protein-

Structure of the spike-The coronavirus spike protein is a type I glycoprotein that forms the peplomers on coronavirus particles. (Figure shows linear diagrams of several coronavirus spike proteins.) Some coronaviruses spikes (most from group II and III viruses) are cleaved into two subunits by a furin-like enzymatic activity during processing in the Golgi. The prototype MHV spike is 180 kDa; for most MHV strains, it is cleaved into two noncovalently associated subunits of about 90 kDa [31]. The amino-terminal S1 subunit, which is believed to form the globular head of the mature protein, contains a receptor binding domain (RBD) within the first 330 amino acids[32]. The RBDs of HCoV-229E (residues 417 and 547) and SARS-CoV (residues 318 to 510) spikes are also found in S1, although not at the amino termini (Fig.no 03).[33,34]. S1 of MHV contains, downstream of the RBD, a “hypervariable domain” (HVR) that varies in length among strains. Comparison of sequences of various isolates of the JHM strains as well as one

isolate of the A59 strain shows "in-frame" deletions of up to 450 nucleotides (relative to the MHV-4 isolate of JHM) in the HVR[35]. The carboxy-terminal S2 subunit, which is conserved among all coronavirus spikes and is believed to form a stalk-like structure anchored in the membrane, contains two (or perhaps three) heptad repeat (HR) domains as well as the putative fusion peptide[36,37,38,39]. A cysteine-rich domain that bridges the putative junction of the anchor and the cytoplasmic tail is necessary for fusion, as is the transmembrane domain[40]..

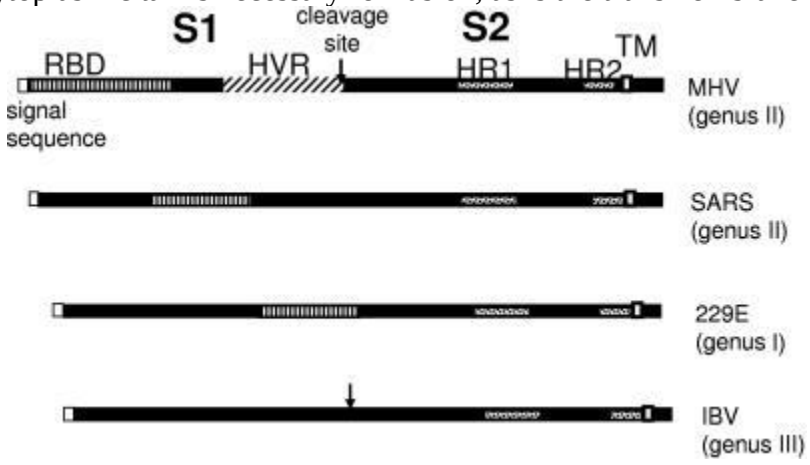


Fig no. 03 Schematic of coronavirus spike proteins. Shown are spike proteins representative of those of all group I to III coronaviruses and of SARS-CoV. The coronavirus spike protein is synthesized as a precursor, cotranslationally glycosylated, and, in some cases, cleaved in the approximate middle into S1 and S2 subunits at a site with dibasic amino acids (BBXBB). S1 forms the external domain containing the receptor binding domain (RBD) at its 5′ end, followed by, in the case of MHV, a hypervariable domain (HVR). A short signal sequence in cleaved from the 5′ end of the mature protein. S2 is the transmembrane subunit containing two heptad repeats (HR1 and HR2) and the transmembrane (TM) domain.

TREATMENT & PROTECTION

In general, there are few or no treatment options for viral diseases that occur suddenly.[41] In parallel with this knowledge, today there is no vaccine or effective treatment to prevent COVID-19 infection. Molecules are being tested for COVID-19 in in-vitro and human-based SARS-CoV and MERS-Cov trials. Studies evaluating the antiviral activity of types I and II interferons have reported, interferon-beta (IFNb), as the most potent interferon, was reducing in- vitro MERS-CoV replication.[42] According to a human MERSCoV case report from South Korea, the use of the combination of Lopinavir/Ritonavir (LPV/RTV) (Anti-HIV drugs), pegylated interferon and ribavirin provided a successful viral clearance. For this purpose, a randomized control trial (MIRACLE Trial), that aimed to determine whether LPV/RTV-IFNb improved clinical results in MERS-CoV patients, was initiated in 2016 and 76 patients were enrolled. [43] Although another antiviral drug, remdesivir was used in the first case reported from the United States of America, seemed successful, controlled studies with more cases are needed. In-vitro studies have shown that viral RNA transcription was terminated with remdesivir in early stage.[44,45] There are publications demonstrating that remdesivir has a strong antiviral activity in epithelial cell cultures against SARS-CoV, MERS-CoV and related zoonotic bat CoVs.[46,47]

Many measures should be taken, such as timely publication of epidemic information for elimination of the source of infection, early diagnosis, reporting, isolation, supportive treatments and for avoiding unnecessary panic. CDC reminds basic measures such as hand washing, using disinfectant solutions, avoiding contact with patients in order to prevent the spread of viruses by droplets. Precautionary actions including the provision of medicines supply chains, personal protective equipment, and hospital supplies should be made in a short time for the protection of the Chinese people and global health, especially in the places with close travel ports to major Chinese ports.[47]

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. As bats seem to be a significant reservoir for these viruses, it will be interesting to determine how they seem to avoid clinically evident disease and become persistently infected. Second, many of the non-structural and accessory proteins encoded by these viruses remain uncharacterized with no known function, and it will be important to identify mechanisms of action for these proteins as well as defining their role in viral replication and pathogenesis. These studies should lead to a large increase in the number of suitable therapeutic targets to combat infections. Furthermore, many of the unique enzymes encoded by coronaviruses, such as ADP-ribose-1”-phosphatase, are also present in higher eukaryotes, making their study relevant to understanding general aspects of molecular biology and biochemistry. Third, gaining a complete picture of the intricacies of the RTC will provide a framework for understanding the unique RNA replication process used by these viruses. Finally, defining the mechanism of how coronaviruses cause disease and understanding the host immunopoathological response will significantly improve our ability to design vaccines and reduce disease burden.

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Conflict of Interest

The author declared no conflict of interest.

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