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Comparative Study of SARS-CoV-1, SARS-CoV-2 and MERS-CoV Protein Structure

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ABSTRACT

The novel coronavirus (SARS-CoV-2) pandemic of 2019 has triggered a global health emergency. The spread of this virus has raised a number of concerns about its transmissibility, impact, and risk factors. To better understand this, we conducted a comparative study of the biochemical structures of three pathogenic viruses that primarily attack the respiratory system: SARS-CoV-2, severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). This comparative study evaluates the structure of these viruses. Because the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 is still ongoing, this evaluation may help public health officials and medical experts slow the pandemic's spread.

Keywords: COVID-19, SARS, MERS, coronavirus, immune system, nucleotides.

I. INTRODUCTION

Now Coronaviruses are a large family of viruses that cause respiratory illness ranging in severity from the common cold to fatal pneumonia. Numerous coronaviruses, which were first discovered in domestic poultry in the 1930s, cause respiratory, gastrointestinal, liver, and neurological diseases in animals. Only seven coronaviruses have been identified as causing disease in humans. Four of the seven coronaviruses most commonly cause common cold symptoms. Coronaviruses 229E, OC43, NL63, and HKU1 account for 15 to 30% of common cold cases. Severe lower respiratory tract infections, such as bronchiolitis and pneumonia, can occur in rare cases, primarily in infants, the elderly, and the immunocompromised. Three of the seven coronaviruses cause much more severe, and sometimes fatal, respiratory infections in humans than the others, and have caused major outbreaks of deadly pneumonia in the twenty-first century. Their infections cause diseases ranging from mild respiratory illness to acute pneumonia and even respiratory failure. SARS-CoV-2 is a novel coronavirus that was first identified in Wuhan, China in late 2019 as the cause of coronavirus disease 2019 (COVID-19) and spread worldwide. MERS-CoV was identified in 2012 as the cause of Middle East respiratory syndrome (MERS). SARS-CoV was identified in 2003 as the cause of an outbreak of severe acute respiratory syndrome (SARS) that began in China near the end of 2002.

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II. SARS-COV-1 STRUCTURE

Severe acute respiratory syndrome (SARS) was first detected in China in late 2002. A worldwide outbreak occurred, resulting in more than 8,000 cases worldwide, including Canada and the United States, and more than 800 deaths by mid-2003. The SARS-CoV genome is about 29,700 nucleotides long and contains at least 14 functional open reading frames (ORFs) that encode 28 proteins in three categories: two large polyproteins (pp)1a and (pp)1ab that are cleaved into 16 non-structural proteins required for viral RNA synthesis (and likely other functions); four structural proteins (the S, E, M, and N-proteins) required for viral assembly; and eight accessory proteins that are thought to be unimportant in tissue culture but may provide a selective advantage in the infected host (Figure 1) [4].

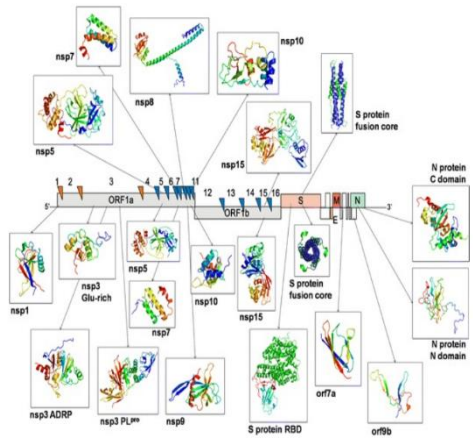

Figure 1 : Summary of SARS-CoV-1 structures

The SARS-CoV replicase gene encodes 16 non-structural proteins (nsps) with multiple enzymatic functions [5]. These are known or are predicted to include types of enzymes that are common components of the replication machinery of plus-strand RNA viruses: an RNA-dependent RNA polymerase activity (RdRp, nsp12), a 3C-like serine protease activity (Mpro or 3CLpro, nsp5), a papain-like protease activity (PL2pro, nsp3), and a superfamily 1-like helicase activity (HEL1, nsp13). In addition, the replicase gene encodes proteins that are indicative of 3′-5′ exoribonuclease activity (ExoN homolog, nsp14), endoribonuclase activity (XendoU homolog, nsp15), adenosine diphosphate-ribose 1″-phosphatase activity (ADRP, nsp3), and ribose 2′-O-methyltransferase activity (2′-O-MT, nsp16). The SARS-CoV genome encodes four structural proteins that are required to drive cytoplasmic viral assembly: the spike (S) protein, the membrane (M) protein, the nucleocapsid (N) protein and the envelope (E) protein. The S-protein is mainly responsible for binding to the host cell and for subsequent cell entry by virus-cell membrane fusion.

Infection with SARS-CoV can trigger a series of humoral and cellular immune responses. Specific antibodies against SARS-CoV (immunoglobulin G (IgG) and IgM) were detectable approximately 2 weeks post-infection, reaching a peak 60 days post-infection and remaining at high levels until 180 days post-infection [6]. High titres of neutralizing antibodies and SARS-CoV-specific cytotoxic T lymphocyte responses were detected in patients who had recovered from SARS [7,8] and the levels of the responses correlated well with the disease outcome. This suggests that both humoral and cellular immune responses are crucial for the clearance of infection by SARS-CoV.

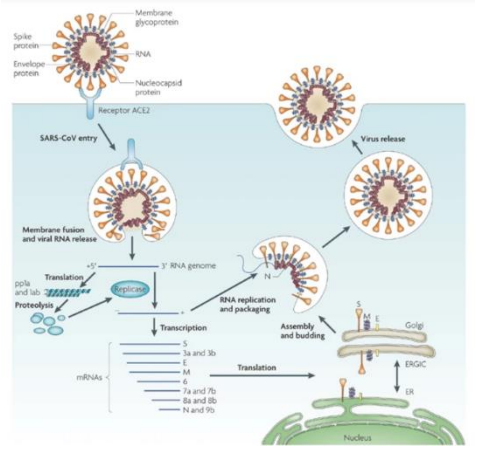

Figure 2: The life cycle of SARS-CoV in host cells

III. SARS-CoV-2 STRUCTURE

The structure of SARS-CoV-2 S protein resembles the closely related SARS-CoV S protein. Initially, the Coronaviridae Study Group of the International

Committee on Taxonomy of Viruses identified this virus as a sister clade to the prototype human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species severe acute respiratory syndrome-related coronavirus. Later, it was labeled as SARS-CoV-2.

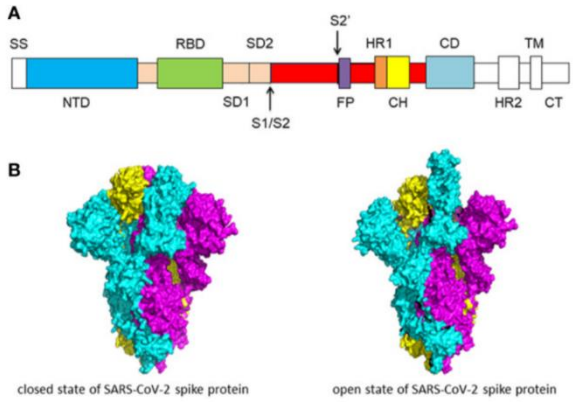

Figure 3: Schematic of SARS-CoV-2 spike protein

The genome of CoVs (27–32 kb) is a single-stranded positive-sense RNA (+ssRNA) which is larger than any other RNA viruses. The nucleocapsid protein (N) formed the capsid outside the genome and the genome is further packed by an envelope which is associated with three structural proteins: membrane protein (M), spike protein (S), and envelope protein [11]. As a member of coronavirus family, the genome size of SARS-CoV-2 which was sequenced recently is approximately 29.9 kb. SARS-CoV-2 contains four structural proteins (S, E, M, and N) and sixteen non-structural proteins (nsp1–16). Nsp1 mediates RNA processing and replication. Nsp2 modulates the survival signaling pathway of host cell. Nsp3 is believed to separate the translated protein. Nsp4 contains transmembrane domain 2 (TM2) and modifies ER membranes. Nsp5 participates in the process of polyprotein during replication. Nsp6 is a presumptive transmembrane domain. The presence of nsp7 and nsp8 significantly increased the combination of nsp12 and template-primer RNA. Nsp9 functions as an ssRNA-binding protein. Nsp10 is critical for the cap methylation of viral mRNAs. Nsp12 contains the RNA-dependent RNA polymerase (RdRp), which is a critical composition of coronavirus replication/transcription. Nsp13 binds with ATP and the zinc-binding domain in nsp13 participates in the process of replication and transcription. Nsp14 is a proofreading exoribonuclease domain. Nsp15 has Mn(2+)-dependent endoribonuclease activity. Nsp16 is a 2'-O-ribose methyltransferase [12].

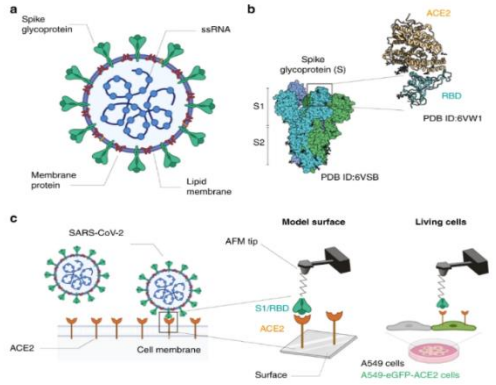

Figure 4: SARS-CoV-2 binding to the host receptor

IV. MERS-CoV STRUCTURE

The MERS virus was first detected in Jordan and Saudi Arabia in 2012. As of early 2018, there were 2,220 confirmed cases of MERS and 790 deaths. Most occurred in Saudi Arabia, where new cases continue to appear. Cases have also occurred in countries outside the Middle East, including France, Germany, Italy, Tunisia, and the United Kingdom in people who had been traveling or working in the Middle East.

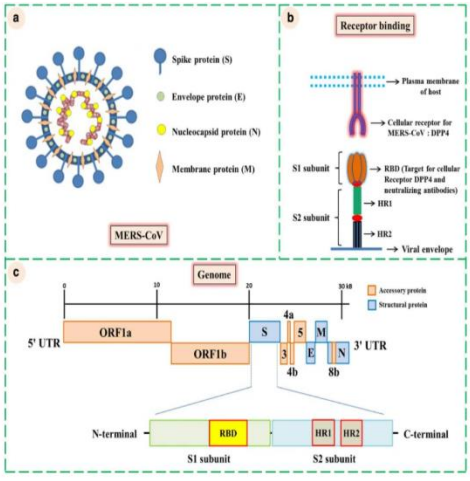

Figure 5: Schematic structures of MERS-CoV proteins

The genomic profile of MERS-CoV is over thirty thousand nucleotides in length, with seven predicted open reading frames (ORFs) (ORF1a, ORF1b, ORF3, ORF4a, ORF4b, ORF5 and ORF8b) and four structural genes (S, E, M, N) [13,14]. The two ORFs (ORF1a, ORF1b) encodes replicase complex whereas remaining five accessory ORFs encodes five accessory proteins which play a crucial role in the infection and pathogenesis. The four structural genes viz., S, E, M, N encodes spike, envelope, membrane and nucleocapsid protein, respectively [13,14]. Spike protein is located on the surface. It has been established to be one of the significant factors in their zoonotic transmission through virus-receptor recognition mediation and subsequent initiation of viral infection. The S protein of MERS-CoV is a transmembrane protein having two subunits S1 and S2. The S1 subunit has a receptor-binding domain (RBD) that binds with dipeptidyl peptidase 4 (DPP4) receptor of the host. MERS-CoV utilises cellular DPP4 receptor of the host for cell entry through binding of its S protein [15]. The main membrane fusion unit is formed by heptad repeats H1 and H2 of S2 subunit [80]. The envelope (E) protein has its role in assembly, intracellular transport and budding of MERS-CoV whereas the membrane (M) protein is required for viral assembly and morphogenesis. All four structural proteins viz. N, S, E and M proteins interact together to form a complete virus particle [83]. Binding of S protein of MERS-CoV to the host cellular receptors results in attachment and start of an infection. This is to follow by fusion of viral envelope with host cell membrane triggered by cleavage of S proteins facilitated by cellular proteases. Hence the availability of these cellular proteases after receptor attachment is considered as the main step determining viral entry.

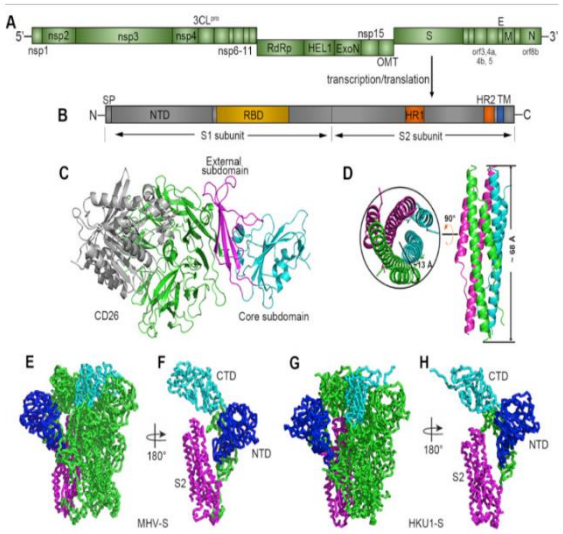

Figure 6: Genome arrangement of MERS-CoV

Studies on an IFN-stimulated gene (ISG) expression in Calu-3 human respiratory epithelial cells has further established the capability of MERS-CoV to hide from the host immune system. Cells infected with MERS-CoV have affected chromatin structures which result in the inability of transcription factors to reach and bind with some ISG promoter regions. The mechanism for this alteration is still under investigation; however, it is suggested that an epigenetic mechanism may be involved in alteration of the structure of chromatin, disrupting the expression of genes in the host.

V. CONCLUSION

The structures of proteins will aid in elucidating their functions, many of which were previously unknown, and will serve as a crucial starting point for understanding the coronavirus replication and transcription mechanism, which is unique and complex. Second, the new fold information offered by SARS-CoV structures will aid in the study of several new protein families' structure–function interactions. Third, the presence of SARS-CoV structures gives targets for structure-based antiviral drug development for therapeutic intervention. A stockpile of anti-

coronaviral drugs could provide an effective first line of defence if another coronavirus emerges.

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