Review Article

Covid-19 origin, transmission, immune response and treatment: A review

Anfal Al-ajmi[1], Arwa Saleh Bazighifan[1], Salman Alamery[1], Seema Zargar[1*]

[1]Department of Biochemistry, College of Science, King Saud University, Riyadh, 11451, Saudi Arabia

[*]Corresponding author email: **szargar@ksu.edu.sa**

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Abstract

The novel 2019 Corona viruses are enveloped RNA genome virus, with a 79% genome similarity to the previous 2003 SARS Coronavirus-1 (SARS-CoV-1). Up to date the confirmed cases worldwide 11,327,790 And 209,509 in Saudi Arabia. The SARS-CoV-2 is a single strand RNA belongs to Beta corona virus. The phylogenetic analysis suspected that bats are the primary reservoir, however the zoonotic intermediate host that transfer SARS-CoV-2 to human is not identified. The glycoprotein spike exclusively on the SARS-CoVs-2 species binds to the host cell receptor through a region called receptor-binding domain (RBD) and mediates viral entry. SARS-CoV-2 targeting Angiotensin-converting enzyme 2 explain the reason behind the infection of the respiratory system especially. S glycoprotein is the most important protein of the virus while it is the best target for entry inhibitors, neutralizing antibody, and vaccine development. Besides the role of antibodies to eliminate virus separation, it can also reas viral entry in some virus species through a mechanism termed antibody-dependent enhancement (ADE) under certain conditions. This mechanism is the main block in the way of vaccine development against SARS-CoV 2. The balance between getting the induction of immunity protection and developing an enhanced susceptibility to virus infection after vaccination against SARS-CoV-2 is a highly sensitive and delicate approach and has a high risk. This novel version of the virus has many routes for infection, this may describe its ability to spread at a high rate and its high aggressivity compared to the previous one every year.

Key words

Covid-19, Origin, Transmission, Immune response, Treatment, Review.

Introduction

Corona viruses are enveloped viruses with unusually large of 26 to 32 kb plus-strand RNA genomes, belongs to subfamily Orthocoronavirinae classified according to International Committee of Taxonomy of Viruses (ICTV). From 2002 to 2003 a member of human betacoronavirus severe acute respiratory syndrome (SARS) has circulated temporarily in the human population resulting in an epidemic of SARS, with a 10% case fatality rate [1].

On 30 December 2019, samples collected from three patients with pneumonia of unknown etiology were analyzed to reveal that the pathogen belongs to betacoronavirus and the whole genome sequence of the virus shows that the closest genome sequence similarity was with the bat SARS-like corona virus strain Bat-Cov RaTG13, identity 96% [2]. According to the daily report of the World Health Organization, the confirmed cases have been reported were reside from 282 cases to 11,327,790 cases and a 532,340 death cases in the interval from the 20th of January to the 6th of July 2020. And 209,509 cases until the 6th of July in Saudi Arabia [3, 4].

Symptoms of disease included Fever, dry cough, shortness of breath tiredness, and diarrhea with occasional loss of taste or smell. These symptoms usually are mild and begin gradually, it appears from 2 to 14 days after infection while as some infected people do not develop any symptoms and do not feel unwell. Around 1 out of every 6 people who are infected with COVID-19 face critically ill but most of the patients (80%) recover from the disease with little to no medical intervention. Aged and people with underlying conditions are more likely to get serious illnesses [5, 6].

Coronaviruses are divided into four genera: α, β, γ, and δ. Betacoronavirus include the SARS-CoVs and SARS-CoV-2 species. Amongst these there are seven coronaviruses in the minimum that could infect humans. They are classified as HCoV-229E and HCoV-OC43 from α-coronaviruses and SARS-CoV (SARS-CoV-1), HCoV-NL63, CoV-HKU1, MERS-CoV, and the recently described SARS-CoV-2 (nCoV-19) from β-coronaviruses [7, 8].

Genome and protein Structure

The first isolation and identification of the new viral SARS-CoV-2 whole genome was released on 10 January 2020 from case in Wuhan [9]. The nucleic material of SARS-CoV-2 contains a single-stranded RNA ranging in size from 29 to 32Kbs [9, 10]. It shows the typical beta corona virus organization. It comprises of the 5'- and 3′ untranslated region with size of 265 and 358 nucleotides respectively [11]. There are 6 to 12 open reading frames, the open reading frame (orf1ab) is the largest gene and represents two-thirds of viral RNA that is encoding two polyproteins, pp1a and pp1aband 16 non-structural proteins (nsp) including nsp3 (papain-like protease), nsp5 (chymotrypsin-like, 3C-like, or main protease), nsp12 (RNA-dependent RNA polymerase [RdRp]), nsp13 (helicase), and other nsps for transcription and replication. The rest open reading frames orf 3, 6, 7a, 7b, 8 and 9b encode accessory and structural proteins [11, 12]. The four key structural proteins of beta corona virus encoded are S gene (Spike), E gene (Envelope), M gene (Membrane), N gene (Nucleocapsid) [11, 12, 13].

Study of genetic variation among 27 of 2019-nCoV isolated from different places; one in Thailand and three in China (Wuhan, Zhejiang, and Guangdong)revealed that the degree of sequence diversification were small compared to rapid reassortment and mutation of avian influenza (H7N9) [14]. In the other study, on 103 SARS-CoV-2 genomes sequence was downloaded from GISAID, GenBank and NMDC for visualization. They identified two major SNPs that categorizes SARS-CoV-2 to two main types L and S type. The L type was found in ~70% of 103 SARS-CoV-2 virus strains and exhibited a “CT” haplotype and the SNPs at positions 28,144 (ORF8:C251T, S84L) and S type was found in ~30% of strains exhibited as “TC” haplotype at positions 8,782 (orf1ab:

T8517C, synonymous).The L type was reported to be derived from S type and there is no pathogenesis difference in both two types, the mutation in orf1ab does not affect the protein sequence (it alter the codon AGT (Ser) to AGC (Ser)) [15].

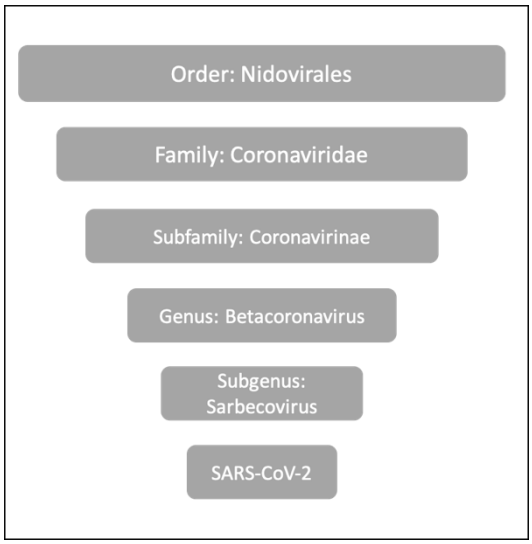
Amongst all alpha- and beta corona viruses, SARS-CoV-2 has two distinctive features in its spike genome. First, mutation in the receptor binding domain (RBD) that result in strong affinity binding to human receptor ACE2.Second, insertion of 12 nucleotides that introduce a functional polybasic (furin) cleavage site with sequence RRARat the junction of S1–S2, the two subunits of the spike glycoprotein [16]. Almost 99% of S2 subunit is similar to human SARS-CoV and bat SARS-like CoVs while the S1 subunit shares around 70% [12]. S1 subunit contains a signal peptide, followed by an N-terminal domain (NTD) and RBD domain at the C-terminal which mediate virus entry via direct binding to host receptor [12, 17]. S2 subunit comprises of fusion peptide (FP), heptad repeat (HR) 1 and 2, transmembrane domain (TM), and cytoplasmic domain (CP) [12]. Another distinctive features at the furin cleavage site is a leading proline inserted that creates a turn that probably leads to the addition of three O-linked glycans to S673, T678 and S686 surrounding the cleavage site. In spite of the fact that the polybasic cleavage site is not discovered in betacoronaviruses lineage B and is observed in other human beta corona viruses lineage A like HKU1 [16].

Origin and the Primary host of SARS-CoV-2

The source and zoonotic origin of SARS-CoV-2 are important for the evaluation of transmission dynamics and preventive action.

From comparative genetic analysis of SARS-CoV-2 with another related SARS-CoV-like corona virus, it was found that the SARS-CoV-2 has mutation in RBD portion of the spike protein and its distinct backbone is different from any other available beta corona viruses [16]. The Phylogenetic analysis of SARS-CoV-2indicates that it belongs to subgenus Sarbeco virus of the genus Betacoronavirus [1].α- and β-CoV hosted only in mammal, while γ- and δ-CoV tend to behostedin birds [11]. All four generaviruses with single-stranded RNA belong to order Nidovirales, family Coronaviridae, subfamily Coronavirinae [9] (**Figure – 1**).

Figure - 1: Taxonomy of SARS-CoV-2.

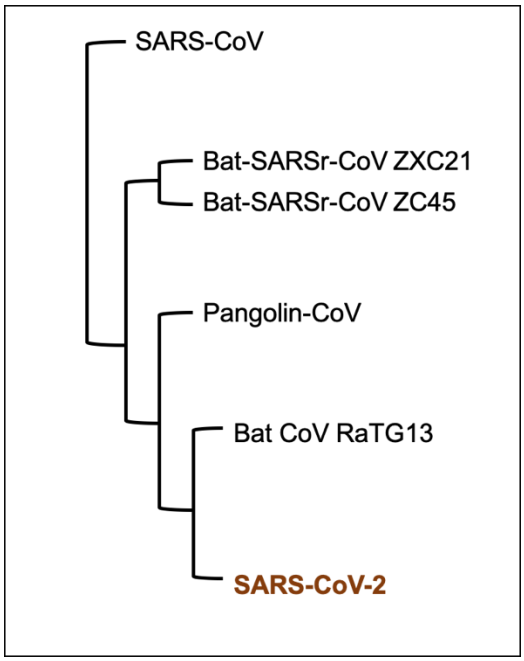


There is a high chance in recombination between the four of them and they have inherently high mutation rates which may increase the possibility to infect new host [18]. From corona virus family, six have been identified to infected human 229E, NL63, OC43, HKU1, MERS-CoV, and SARS-CoV [9]. The novel corona virus disease 2019 is the seventh member and named SARS-CoV-2 because it's genetically related to the severe acute respiratory syndrome SARS-CoV [19].

The complete genome sequence of SARS-CoV-2 from Wuhan patients showed that it is distinct from both SARS-CoV and MERS-CoV that caused epidemics in past by 79% and 50% respectively [1, 20]. While it showed a higher sequence identity with SARS-like beta corona virus of horseshoe bats (Rhinolopus sinicus) origin, bat-SL-CoVZC45 and bat-SL-CoVZXC21, collected in 2018 in Zhoushan city, eastern China with around 88%similarity [1, 13]. Another bat betacoronavirus Rhinolophus affinis from Yunnan ProvinceRaTG13, revealed that it

highly related to SARS-CoV-2 and the similarity among genome sequence was 96% [20, 21, 22]. Examining the whole genome by phylogenetic analysis the 2019-nCov was clustered within lineage 2B, in different clade from SARS-CoV [1]. 2019-nCov and RaTG13 are form a distinct lineage from other SARSr-CoV [20] (**Figure – 2**).

Figure – 2: Consensus Phylogenetic Tree by Whole Genome.



Based on evolution and phylogenetic results to determine the origin of SARS-CoV-2, it was suspected that bats could be the original host [1, 12]. Further phylogenetic investigation of the receptor-binding domain in spike regions showed bat is not the direct origin [12, 21]. It suggested that either ancient homologous recombination event or random mutations combined with natural selection or both of them, participated in cross-species transmission event [15, 21]. As SARS-CoV and MERS, both originated from bats and transmitted to human by civet in SARS and camel in MERS [12]. SARS-CoV-2 could be transmitted from bats to human via unknown intermediate hosts that might be one of wild animals or mammals sold in seafood market in Wuhan [14].

Several studies have been reinvestigated the published data of corona viruses isolated from Malayan pangolins (Manis javanica) that were illegally smuggled to Guangdong province on 2019 and found that it was comparable to SARS-CoV-2 with whole genome sequence by 91% [22, 23]. Even though the RaTG13 was the closest to SARS-CoV-2,one amino acid of the six critical amino acid residues in RBD region of SARS-CoV-2 was similar (89.2% amino acid similarity in RBD), while Pangolin-CoV was identical to all six-amino acid (97.4% amino acid similarity in RBD) [15, 24]. The aligned genome sequences showed no recombination events between RaTG13 and SARS-CoV-2 and yet likely recombination with Bat_SARS-like corona virus [20, 21]. It was suggested that Pangolin-CoV might be the common ancestor of SARS-CoV-2 and RaTG13 and it also suggested that might be the origin of RBD in spike gene to SARS-CoV-2was a result from recent recombination events in Pangolin with a Bat-CoV-RaTG13-like virus [22, 23]. Pangolins and bats are both active at night, eat same food, which makes them best possible zoonotic intermediate [23]. Despite that, neither Pangolin-CoV nor the bat beta corona viruses had S1/S2 cleavage site in the S protein [16]. It is proposed that the similarity with SARS-CoV-2 in the amino acid in RBD region of Guangdong pangolin corona viruses can be coincidental approximate natural evolutionary process and not necessarily recombination, and if any recombination events happen it could be around 19.8 to 55.4 years ago, which means that these animals could be long-term reservoir hosts for these viruses [15, 16, 24]. Striking theory of origin of SARS-CoV-2, proposed that many prior zoonotic events transmitted to human and gained the polybasic cleavage site via adaptation during undetected human-to-human transmission, which lead to pandemic outbreak once the virus acquired these adaptations [16], Same scenario that happened in MERS-CoV [16]. Further investigations of a wide range of possible virus reservoir animals that sale in Hunan seafood market is needed to determine the intermediate zoonotic source of the virus.

Corona virus and host cell infection

Coronaviridae family encodes a surface glycoprotein, spike, which binds to the host cell receptor and mediates viral entry. But specially β-CoVs encode a region called receptor-binding domain (RBD) on its glycoprotein spike that enables its interaction with the host cell receptor. Host protease enzyme releases the spike fusion peptide after the binding of the virus to the cell receptor resulting in virus entry. Angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) are the known host receptor for β-CoVs SARS-CoV and MERS-CoV respectively. This binding explains β-CoVs targeting mainly the respiratory system cells as these cells mainly express this kind of receptor. Additionally kidney and gastrointestinal tract also express ACE 2 receptors so there is a chance of infection to these tissues in the patient. Also, because of the receptors present this leads to the chance of infection by fecal-oral route and body fluid (urine) beside the inhalation route. The ACE 2 receptor approach may be helpful in the treatment of the SARS either by blocking the S-protein-binding site or by inducing a conformation in ACE2 that is unfavorable to binding or fusion [25, 26]. Unfortunately until now there is no effective therapeutic agent available for either the treatment or protection against corona virus infection despite the tremendous efforts of scientists around the world [27].

The single glycoprotein spike is a homotrimer composed of three receptor binding S1 subunits and a trimeric membrane fusion S2 stalk, with the RBD placed on the tips of these three subunits. RBD is presented in two forms, on the mature virions it is in the standing-up (prefusion) state which is stabilized by the binding to the cell receptor. This binding also leads to the enhancement of a conformational change mediated by host protease that cleaves the two sites sequentially: first at the S1/S2 boundary and then within S2. After protease cleavage S1 subunit detaches while as the S2 subunit will undergo a structural change that will mediate viral fusion into the host cell , this is called the 'postfusion' state which is the second state of the RBD [25]. S protein is the most important protein among the other Corona virus structural and non-structural proteins as it plays a role for virus-cell entry and provide an significant target for Entry inhibitors, neutralizing antibody, and vaccine development [28].

Immune responses and Antibody-dependent enhancement

The Humoral and cellular immune responses activated by the highly antigenic structure of the virus surface works to extirpate viruses in the host. Antibodies are the effective agents that neutralize the viruses and reduce its infectivity by targeting the glycoproteins that are represented on the surface of enveloped viruses and the protein shell of non-enveloped viruses, there are two models described for the kinetics of neutralization. The first model is the single-hit model, where it postulated that a single antibody is sufficient to neutralize the virus when it binds to a critical site on the virion. The second model is the multi-hit model, which is the most accepted model. This model proposes that neutralization is only achieved once an individual virion is bound by several antibodies which exceed the stoichiometric threshold of neutralization. To determine the stoichiometric threshold of neutralization it depends on antibody affinity and the epitope accessibility. Paradoxically, however, occasionally virus uptake inside the cell is thought to be improved by a mechanism termed Antibody-dependent enhancement (ADE) either by a sub-neutralizing concentration of the antibodies or by the non-neutralizing antibodies under certain conditions that enhance viral entry into the host cells [29].

This ADE enhances viral pathogenicity by increasing viral entry into the host cells and presents an important relationship with the neutral pathogenesis of some viruses. As an example, the Dengue virus (DENV, a member of the Flaviviridae family), severe disease symptoms had emerged in the infant whose maternal antibody level against DENV had

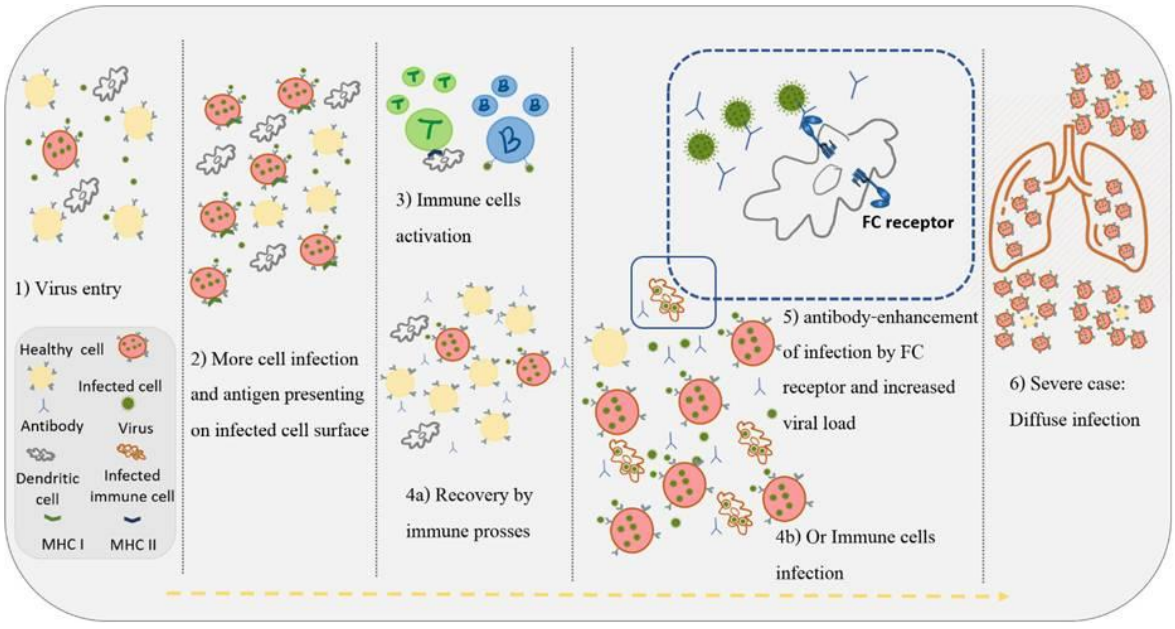
declined to a low level, a sub-neutralizing level of the antibodies [30].

Developing an effective vaccine against SARS-CoV-2 is a high challenge and has a high risk to patients of getting enhanced susceptibility to infection after vaccination and advance the clinical symptoms of the disease, this risk is a large stumble block in the way of reaching an effective vaccine and therapy development. Huisman, et al. reported that the balance between getting the induction of immunity protection and developing an enhanced susceptibility to virus infection after vaccination is a highly delicate approach [30]. Ade., 2019 compared the mortality rate of vaccinated SARS-CoV-1 and SARS-CoV-2 patients before and after day 14 of infection, they found the morality rate percentage decreased when it was provided before day 14 (6.4% mortality rate) [31]. This suggestion could be supported by the study of Wang et al who reported that starting with a low level of antibody concentration for immunization resulted in an opposite result to the expectation [32].

Table – 1: The reported number of confirmed COVID-19 cases and deaths in some Countries with high median age. Data as of 10 AM CEST, 12 July 2020.

Country	Population [36]	Median age (years) [36]	Confirmed cases[37]	Deaths [37]
SPAIN	**46,755,366**	**44.9**	253 908	28 403
IRAN	**84,021,254**	**32.0**	255 117	12 635
FRANCE	**65,278,075**	**42.3**	161 275	29 907
ITALY	**60,458,858**	**47.3**	242 827	34 945
CHINA	1,439,494,919	38.4	85 522	4 648

Figure – 3: Virus separation and Immune cell response. 1) Virus entry to the host cell via ACE 2 receptor. 2) The infected cells presented antigens while virus separation. 3) Immune response by immune cells activation and antibodies release. 4) Then the recovery will happen by immunity (4a) or an opposite result by immune cells infection (4b). This ends with a further severity in cases (5).



SARS-CoV-2 has many routes of infection and this may describe its ability to spread at a high rate and its high aggressivity compared to SARS-CoV-1. Besides that, corona viruses exploit antibody Fc uptake of the immune responses to infect immune cells (**Figure - 3**), it could also use the subunit 2 FP, HR1, and HR2 of the glycoprotein S within the endosomes to infect

immune cells during proteolytic cleavage processes. Viral infection of complement receptor (CR) cells is another possible way of cell infection. Depending on this multi-pronged approach, the antibody-mediated uptake hypothesis, can be applied to the situation of SARS-CoV-2 which induces ADE either by vaccination or maternally transferred antibodies (matAbs). The progression of the disease from mild-flu symptoms to moderate and severe symptoms often coincides with the activation of the humoral immunity and the patients may acquire immune cell infection which leads to multiplied symptoms of the disease, postulates the mechanism of immune cell infection [31, 33]. COVID-19 severity and its discrepancy among different regions could accrue because of the higher median age of the population (**Table - 1**). Besides that, there are some other reasons, Antibody-dependent enhancement could be an explanation where the individuals in the areas with high severity and mortality rate may have a prior exposure to another serotype such as the prevalence of the four corona viruses (HCoV-OC43, 229E, NL63 and HKU1) before SARS-2 epidemic in a countries with high mortality reports was as following: 2.4% (Spain), 5.5% (Iran), 9.3% (France), 10.5% (Italy) and 23% (China). And these countries have a high mortality rate in the percent statewithCOVID-19epidemic see (Table.1)except China where it has the lowest confirmed cases and the lowest mortality rate among these countries, this could be a result of ADE through the previous serotype-specific antibody's [34]. A suppression of antiviral genes (such as tumor necrosis factor and inducible nitric oxide synthase) expression where shown in the case of Ross River virus and DENV viruses cross the infection of macrophage cells through the FC receptor, which is the mechanism of ADE, in contrast the infection by the normal target receptor dose not effect this antiviral genes [30, 35].which may happen in the case of COVID-19 ADE infection as both shared the same mechanism.

In addition, it was Postulated that the Geographic discrepancy of cases severity may happened by ADE as it approved by many studies in in-vivo and in in-vitro of SARS-CoV-1,and found that it hider the ability of the immune cells and inflammations. Where ADE also have been hypothesized to be the reason for the high mortality rate in china in 2005 [38]. Wang, et al. revealed that enhancement may be improved by increasing dilutions of antibodies, suggesting a temporal relationship between priming and enhancement [32]. But his study rejected by Luo, et al. study results, where they used inactivated whole SARS-CoV Z-1 vaccine to investigate if the low level of antibody concentration could cause ADE when re-infection occurs, they vaccinated a rhesus macaque followed by challenge with SARS-CoV NS-1 virus. Their results showed that the low level of antibody may not induce ADE in rhesus macaques and the vaccine could be a good candidate for clinical trials [39]. The COVID-19 pandemic is still posing a severe threat despite the comparative decrease in the number of cases during September-November 2020, the number of active cases is on the rise again in 2021 and 2022. Recently there are spike in number of cases from China and India.

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