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Insight In The Molecular Structure (spike proteins)/Mechanism of Pathogenesis Against Human Corona Viruses, The Emerging SARS-CoV2 Pandemic; A mini-review

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***Abstract*— Since the emergence of human type, epidemic corona virus infections SARS-CoV and MERS-CoV outbreaks in addition to the present time SARS-CoV2 outbreaks global researchers and medical specialist efforts are continued mining for specific antiviral agent or vaccine against these rapidly spreading lethal infections. Despite the past and nowadays claims here and there for declaring finding of a feasible and safe coronavirus specific antiviral agent or vaccine arguing between specialists are still ongoing however none of these claimed antiviral agent or vaccine are approved by the FDA. Hence, until now no specific antiviral agent or vaccine are authenticated globally to counteract these seriously hazardous coronavirus outbreaks. Within, the last decade and the past few months after the covid-19 pandemic outbreak through the mining of already known antiviral drugs, clinically used drugs for repurposing and Insilco screening of natural and synthetic compounds are ongoing mission to fasten up the process of drug discovery especially after the current COVID-19 outbreak. However, no rational treatment regimen can be established unless a good understanding of the viral pathogenesis mechanism and the critical biomolecules involved have been considered. Hence, under the urgency of new drug discovery, this survey covers some of the molecular targets antiviral drug intervention strategy against this novel coronavirus.**

Keywords*— *coronavirus; pathogenesis; cell entry mechanism; SARS-CoV2; spike protein, potential targets.

I. INTRODUCTION

Within the twenty-first century, the global demand for protein sources as food and commercial products had given rise to the contact and handle different varieties of wild mammalian primates and their viruses without bio-protection. This unsecured contact had led to the jump of zoonatic viruses as in the case of corona viruses to cause serious human infections [1,2]. There are seven types of coronaviruses that can infect human beings and develop an infection. Two strains belong to alpha-coronaviruses: human coronavirus 229E (HCoV-229E) and human coronavirus NL63 (HCoV-NL63, New Haven coronavirus) while, other four types belong to beta-coronaviruses human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) [3-10]. Excluding the three epidemics/pandemic human outbreak causing strains; the four other strains HCoV-229E, HCoV55-OC43, HCoV-NL63, and HCoV-HKU1 cause mild to the moderate common cold-like respiratory infection to humans [11,7]. However, up-to-date researchers consider SARS-CoV-2 is more likely to be resulted from natural selection process that happened either in an animal host or human one after zoonotic transfer [12].

The first jumping corona virus to cause epidemic viral infection in the new millennium was severe acute respiratory syndrome coronavirus SARS-CoV that happened in South Asia [13]. The uncovered inter human's transmission through contact hospital care and traveling had led to a fast transmission of infection of more than eight thousand infections with mortality rate about 10% that left an impact on the economic, life style and health system of some countries especially china in 2003 [7,14,15]. Genomic analysis of SARS-CoV virus had revealed that it is a single stranded, positive-sense RNA virus of large genome size (about 29.7 kb in length) [15]. The botanical analysis had shown that this virus is extremely resembling bat SARS-CoV detected in horseshoe bats. Since then, a globally profound

proposal of future outbreaks possibility is alarmed by so many scientific and health societies if the suitable conditions for the contact, mutation, and transmission are fitted [7,15,16]. The first outbreak of SARS-CoV virus had reported in southern of china during November 2002 in Guangdong Province. The infection then eventually transmitted to 37 countries including neighboring Asian countries, North America and Europe causing about 8270 cases of infection (majorly in china and Hong Kong) with 775 death pathogen resulting in 9% fatality rate [17]. The WHO had reported close estimations of conformed infected cases and deaths with a mortality rate of 9.6% up to April/2020 (www.who.int).

The second epidemic outbreak of human type corona virus impacted after SARS-CoV outbreak that jumped to become a major human pathogen of significant morbidity and mortality was the Middle East Respiratory Syndrome coronavirus (MERS-CoV [18,19]. MERS-CoV has first been discovered in Saudi Arabia in 2012 however, detected antibodies to the same virus strain was found in earlier (1990) isolated sera from dromedary camel/Eastern Africa however, bat was still accused as a jumping source [20-25]. Since then, MERS-CoV infection has spread to about twenty-seven countries up to 2019 (in continuously occurring secondary outbreaks majorly in the gulf Arabian countries as endemic regions) of a total conformed cases of about 2470 primarily reported from the Arabian Peninsula about 85% of them either originated or passed through Saudi Arabia. The second MERS-CoV outbreak that happened outside the Arabian Peninsula was in South Korea in 2015 where a vast majority had passed the Arabian Peninsula through travelers or something other transmission aspect causing a secondary outbreak [26-31]. However, this strain of human coronavirus was more dangerous and of bad morbidity causing 584 death of 1621 laboratory conformed cases up to the end of 2015 with mortality rate of 36% in the second (Asian countries) outbreak [32]. The WHO had reported conformed 2,494 laboratory positive cases of which 858 ends with death with the fatality rate of 34.4% (www.who.int) up to the beginning of April/2020. MERS-CoV virus is an enveloped virus that occurs as spherical particle 118-136 nm size with 16-21 nm spike proteins projecting outside the virus envelope however, its nucleocapsid containing the genetic materials occurs in a flexible helical shape that forms coils folding back on themselves [20, 21, 33].

In December 2019 a third more virulent novel corona virus strain as human pathogen known as COVID-19 or SARS-CoV2 infections had been reported in Wuhan, China; Hubei province. Since china had reported this outbreak, it was declared as a global pandemic by the world health organization WHO [34]. The virus infections continue to spread and to be reported globally by the countries and WHO to reach close to 6,513,301 cases, and more than 386,100 deaths up to 4th of June 2020 according to WHO count released official reports [35]. However, one statistical estimation to the globally reported infection/ mortality data claimed that the fatality rate up to February 2020 was 5.3%. Others argued this estimation to be an exaggerated ones and estimate [36] 1% mortality rate is more realistic since only those with observed signs and symptoms are tested while the asymptomatic patients or those with mild one is not [37-40]. On the 2nd of July 2020, the WHO database dashboard had reported 10,514,028 confirmed cases about half of which in the two Americas and 512,311 deaths with a mortality rate of about 4.9% (www.who.int) and still counting.

This virus strain is of a slightly larger genome size about 29,903 nucleotides with two untranslated sequences of 254 and 229 nucleotides sequences at the 5'- and 3'- ends respectively (GenBank No. MN908947) [14]. The novel corona virus SARS-CoV2 encodes to spike protein, envelope membrane glycoprotein, nucleocapsid phosphoprotein, a replicase complexes as well as 5 other proteins all are comparable to other human type infectious corona viruses however, this novel strain undergoes cell entry into the victim cell using the human angiotensin converting enzyme 2 (ACE2) which is widely distributed throughout body tissues including the primarily targeted cells; pneumocytes II and other airways cells in additions to other tissues like GIT enterocytes, live, kidneys and neuronal cells…etc. explaining some of the diverse signs and symptoms of the infection, complications, and morbidity [41-43]. Bats (*Rhinolophi sinicus*) are also accused of an animal origin to this virus infection as well as to Malayan pangolin (*Manis javanica*) [41, 44]. Morphologically, SARS-CoV2 has a crown shape peplomer of 70-90 nm) containing a positive type single stranded RNA of 28.8 Kb size (for viruses isolated from Korean patients [45]. However, up to date it is not exclusively established whether SARS-CoV is a naturally occurring virus due to a random selection either in host animals before crossing the line of human-animal species or in humans after zoonotic transfer [12] or occur due to human intervention caused genetic modification.

Signs and symptoms of the three viruses are close to each other. In case of SARS-CoV2 infection signs and symptoms include fever, dry cough, dyspnea, muscle pain in addition to other symptoms such as diarrhea [46]. However, in about 5% of the patients who are with no risk factors mild to moderate infection occurs with mild to moderate influenza like signs and symptoms occur. Other significant ratio of patients is asymptomatic but both two groups may have constant activity and mixing with other individuals in the community to enhance the virus transmission and epidemic doubling in the count of the infected patients within 3-7 days [14,46,47]. The epidemiological study showed that the virus incubation period ranged from 1 to 14 days however the spread of the infection occurs through cough and/or sneezing emitted droplets of the patient that can travel in air for distances more than 7-8 meters as well as contact and contaminated surfaces [14,22,47]. Even though, like SARS-CoV infection; MERS-CoV infection most of the patients was observed to have other comorbidity for the development of infection and complication of the patients' condition [48] which is also remarkable for SARS-CoV2 pandemic.

Variation in the pattern of infections has been identified between the three epidemic coronaviruses SARS-CoV, MERS-CoV and SARS-CoV2 including that even SARS-CoV2 is of lower mortality rate in spite it has faster rate of spread among individuals unlike MERS-CoV which is of a very limited one. SARS-CoV2 have human-to-human spread mainly among mild cases, asymptomatic individuals, or those do not developed symptoms at all as they are within the incubation [38-40,49-53]. SARS-COV2 starts infection in the upper airways of the respiratory system as first residence site through direct contact or flying droplets from the infected individuals before the onset of symptoms. While, SARS-CoV residence site for establishment infection is in

the lower respiratory tract and only those of sever signs and symptoms are involved in infection transmission spread [40,49,50].

Most of the admitted patients of poor prognosis outcomes with deterioration in health conditions like respiratory distress and other cardiac manifestations require intensive care unit admission due to the cytokine storm. Their blood samples reveal incline in blood levels of the pro-inflammatory cytokines like including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα [54]. The biochemical and laboratory analysis of SARS-CoV2 infected patients also showed elevated level of leukocytes, increased level of pro-inflammatory cytokines and chemokines included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA as well as elevated level of C-reactive protein besides elevated value of erythrocyte sedimentation rate [54]. Un like SARS-CoV; most of SARS-CoV2 had developed anti-SARS-CoV2 antibodies in low levels during their long duration of illness [45]. However, convalescent plasma from recovered patient have been reported to be used for treatment of infected patients who showed some sort of clinically accepted outcomes [55]. Therefore, the clinical features and the fore mentioned biochemical investigation results of pro-inflammatory overwhelmed secretion as well as elevated WBCs count indicate the SARS-CoV-2 capability evade the immune surveillance of human being much more efficiently than SARS-CoV1 dose [37]. However, there is an assumption that if the viruses evolve to develop characteristics for evading the host immune surveillance, they will lose some of its infectivity due to the decline in its entry-receptor recognition/binding ability which is a determinant target for the immune surveillance/response as well as therapeutic intervention [45, 56, 57].

A. CELL ENTRY OF CORONAVIRUS

As an enveloped virus coronavirus requires entering inside the victim cell in order to deliver its genetic material thus it depends on the fusion process between their envelops and the victim cell membrane; this process is known as cell entry [58]. These pathogenesis steps and immune surveillance greatly depends from one side on the virus structural parts. The genetic materials of human pandemic stains of coronaviruses SARS-CoV, MERS-CoV and SARS-CoV2 encode to four structural proteins and sixteen nonstructural ones (nsp1–16) besides some other accessory proteins [12]. The processes of cell tropism, pathogenesis and entry fusion process starts with binding of virus glycoprotein projections known as spike proteins (S) and certain victim cell receptor. These spike proteins are of class I structural proteins responsible for the two critical processes in the viral pathogenesis which are; victim cell binding and envelope-membrane fusion. However, the fusion step of cell entry requires huge conformational changes in the spike proteins to be performed. These infectious pandemic strains utilize various types of cell receptors to achieve cell binding process, but the fundamental pathogenesis mechanism aspect is still conserved between these various strains [58]. Despite that MERS-CoV binds to the host cell dipeptidyl peptidase cell membrane receptor; SARS-CoV, and SARS-CoV2 viruses binds to other receptor in the host cells ACE2 receptor through their spike proteins. However, there is a controversy between studies for evaluating the binding affinity of SARS-CoV-2 RBD and SARS-CoV RBD to the human host cells ACE2 receptor. Some studies had claimed that SARS-CoV-2 RBD has higher affinity than SARS-CoV RBD, others claimed equal affinities while the third group had claimed weaker affinity than SARS-CoV RBD. Interestingly, in all strains of coronaviruses the spike protein is composed of two subunits the S1 unit that represent the receptor binding domain of the protein occur at the N-terminal domain (NTD), also known as receptor binding domain (RBD) and the S2 unit that represent the membrane fusion unit occur at the C-terminal domain. The S2 subunit intern is further sub-divided into three functional units; two haptate repeats HR1 and HR2 units as well as the fusion peptide (FP) unit [12].

The location of the RBD in the NTD may determine the virus strain infectivity and its evasion of the immune surveillance. The RBD can be classified into either a standing-up state when it is lying up stream sequence of amino acid in the NTD or a lying-down state when lying down stream. In the case of a standing-up state of RBD a direct virus particle binding to the host cell receptor happens as in case of SARS-CoV while; in the case of SARS-CoV2 the other type of RBD; a lying-down state has been found so it can not form direct binding with host cell receptor ACE2 [12, 59]. Therefore, lying down type RBD viruses like SARS-CoV2 can not bind to the host cell surface receptor unless it is in situ activated by the host cell own enzymes such as host cell surface/endosomal proteases like TMPRSS2 and lysosomal cathepsins. Host proteases activation is a remarkable SARS-CoV2 secondary strategy for preserving its potent infectivity while maintaining its RBD is less accessible to the host defenses hence it can be considered as a significantly valuable determinant for understanding this virus strain pathogenesis, the patient's immune surveillance evasion capablility and for designing therapeutic strategies. However, is unlike SARS-CoV, the other remarkable finding of SARS-CoV2 strain is that its ability to preserves an additional spike protein activation mechanism for cell entry to certain patient's tissues that are of low surface proteases/endosomal enzyme; TMPRSS2 and/or lysosomal cathepsins expression known as furin pre-activation site [59, 60]. This spike protein activation protein increases virus virulence, enhance its infectivity as well as evading the immune surveillance through hiding its RBD that probably leads to a poor recognition by the immune response. Thereby, insufficient immune response was observed in addition to complicating the determination of a feasible therapeutic strategy as it makes this virus is less dependent on host cell activation mechanism [59,61].

Despite this critical role of spike protein furin, SARS-CoV2 virus particles may remain to have unchanged or having a declined efficiency of entry even in some TMPRSS2 and/or lysosomal proteases high expression type of cells in vitro. This can be attributed to the slow rate of spontaneous conformational changes in the spike protein required for entry which completely depends on environmental conditions such as high temperature, physical force, or some chemical factors [60]. However, host cell dependent activation leads to an irreversible structural change in the virus spike protein S2 units that leads to the final required conformation for host cell receptor binding [12]. Hence, to compensate for the two vulnerabilities of host protease dependent entry as well as hidden RBD; SARS-

CoV2 virus relies on enhancing its RBD binding affinity to its receptor ACE2 and furin dependent spike protein pre-activation making its cell entry efficiency comparable to that of SARS-CoV [58,61].

Ultimately, despite the close similarity between MERS-CoV and SARS-CoV in the entry mechanism, however, there are several differences in the entry mechanism steps mostly involve its spike protein structure specificity. First MERS-CoV virus uses a different host receptor DPP4 rather than ACE2 receptor. Secondly, like SARS-CoV2 it has a standing-down state RBD in its S1 unit rather than a standing-up RBD unit in case of SARS-CoV. Thirdly, like SARS-CoV2; MERS-CoV virus entry makes use of two distinct pathways; TMPRSS2 dependent activation of spike protein to liberate its S1 located RBD for host cell receptor binding and endosomal cathepsin L activation [62]. In addition, like MERS-CoV, SARS-CoV2 has a furin dependent additional spike protein activation mechanism like that enhances its entry which also maintains bypassing of the low pH-dependent limitation. It has two furin substrate cleavage sites in its spike protein; S1/S2 interface site and S2 located site; the last site is cleaved upon entry [63].

B. Genome And Structural Variations Between SARS-CoV2 And SARS-CoV Viral Strains Especially In Spike Proteins

The genome of SARS-CoV2 virus is about 29.8 kilobase in size single-stranded positive sense RNA (+ssRNA) containing fourteen open reading frames (ORFs) two of them; ORF1a, ORF1ab that located at the 5'-terminus encoding for polyproteins pp1a and pp1b that include fifteen nonstructural protein (nsp) 1 to 10 and 12-16 of the twenty-seven proteins encoded by the whole viral genome. Beside the nsp four structural proteins are encoded by SARS-COV2 genome (S, E, M, N) besides eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, orf14) [10, 64]. Despite that SARS-CoV2 genome encoding set up is like that of SARS-CoV however, there are some remarkable variations between the two strains [64, 65]. These structural variations include absence of 8a protein in SARS-CoV2; longer 8b protein in SARS-CoV2 (121 amino acids) while it is (84 amino acids) in SARS-CoV while 3b protein is shorter in SARS-CoV-2 (22 amino acids) than in SARS-CoV (154 amino acids) [10, 64].

Recently, a striking Insilco and in vitro study of 1393 genome positions encoding for about 1243 amino acids in two closely related human epidemic coronavirus strains SARS-CoV and SARS-CoV2 to compare 22 proteins structures between them; have revealed that most amino acids (89%) are of differentially conserved positions (DCPs). This means that 13% of the total residues encoded by SARS-CoV2 genome is altered either in type or position as compared to the closest human epidemic coronavirus; SARS-CoV which may affect the structure as well the function of SARS-CoV2 proteins. Remarkably, 2.6% of the DCPs are probably of structural as well as functional impact. These alterations suggest a potential difference in SARS-CoV2 biological behavior (pathogenesis, tropism, and response to drugs) as compared to SARS-CoV; which is also confirmed by in vitro investigation in the same study. Furthermore, 73% of these DCPs are a result of natural evolution process in addition 45% of these DCPs involve exchanging amino acids of similar physicochemical properties involving exchanging hydrophobic amino acids while 30% of these DCPs involve exchanging amino acid of different physicochemical properties (polar-hydrophobic exchange). In addition, the exchange between charged amino acids represent 10% of the total 89% DCPs. Insilco dissecting of SARS-CoV2 genome as compared to that of SARS-CoV have revealed that; the identified DCPs are not evenly distributed throughout these 22 proteins. Six of SARS-CoV2 proteins mostly functional ones; are rich with these DCPs; spike (S) 19.4%, 3a 21.5%, p 6 28.6%, nsp2 28.6%, nsp3 21.3% (papain-like protease) and nsp4 18.8%. However, few DCPs have been identified in the envelope protein (E) as well as ORF1ab encoded nsps like helicase enzyme (0.5% of its residues) in addition to RNA-directed RNA polymerase, 2'-O-Methyltransferase, nsp8 and nsp9 (2% 0f their residues). 525 DCPs have been identified DCPs occurred in the major two virus strains proteins, especially the spike protein and the papain-like protease (nsp3). About 92% of these DCPs located in the interacting surface of these proteins; of which only 45 DCPs are suggested to cause structural and/or functional alterations however, 40 DCPs are buried within proteins structures. In addition, 222 DCPs results in some alterations while other 258 DCPs are not seems to cause a real structural or functional alteration in these proteins [66].

C. Spike Proteins Of Human Coronaviruses SARS-CoV2

SARS-CoV2 virus have the following structural proteins beside other functional ones; spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) proteins and hemagglutinin esterase (HE). Beside its virus crown shape related criteria under electron microscope [67]; the spike protein of this virus is a type I transmembrane glycoprotein also playing a significant role in viral entry to the host cell to establish an infection [68]. Like other epidemic coronaviruses SARS-CoV and MERS-CoV; the spike proteins of this strain are also composed of S1 and S2 units located at amino acid sequence 14–685 at the N-terminal domain but with the insertion of four new amino acids at the S1/S2 boundary region as a major difference from the other human pandemic coronaviruses [5, 69]. The S1 sub-unit in the N-terminal domain (NTD) also contains receptor binding domain (RBD) in which the receptor binding motif (RBM) located while the S2 sub-unit is made of contains fusion peptide (FP), heptad repeats 1 (HR1) and 2 (HR2), transmembrane domain (TM) and cytoplasmic domain (CP). However, the S1/S2 interface occur at the residues R685/S686S1 [69]. The lying down state of RBD of this virus besides other non-structural proteins that help to bypass the innate immune response of the host like other coronavirus species has enabled this strain of the virus to evade the immune response surveillance. This immune evasion may lead to the encountered nonspecific/uncontrolled in addition to insufficient immune response manifested as serious infection spread, long period of incubation and recovery in

addition to significant mortality rate [12,59,70, 71]. The controversy between researchers about the exact mechanism of host immune evasion whether related to the affinity difference between coronaviruses spike proteins RBDs or to the lying down state observation by other groups probably suggests that conformational masking is the more likely possible contributing strategy for its RBD hiding to enable its immune evasion [72]. However, in addition to the capability of SARS-CoV2 to adapt two different conformations [12]; the findings of a recently issued study of origin-independent analysis of various virus sub-strains and location distribution proposed that its RBD has a dynamic and unstable characteristics of the SARS-CoV-2 RBD is the major factor for its variable patient's infection severity [73]. These two characteristics may explain the recovery period as well as the clinical manifestations severity. In addition, the last finding may resolve such controversy and explain RBD-related immune evasion mechanism. Therefore, good understanding of SARS-CoV RBD structure and function provides a feasible understanding to the virus infection targeted tissues, clinical manifestations of (COVID-19) infection, prognosis, and morbidity beside the faced complications during medical interventions. After interaction the two trimeric hapted repeats HR1 (residues 910–988) and HR2 (residues 1162–1206) through a hydrophobic interaction through multiple valine, leucine, and isoleucine residues (V1164, L1166, I1169, I1172, A1174, V1176, V1177, I1179, I1183, L1186, V1189, L1193, L1197 and I1198) available in the HR2 and a hydrophobic pocket of HR1 binding site. The interacted HR1 and HR2 besides a flexible linker (L6, SGGRGG) between them form a hexameric complex in which the parallel helical colis located in the center are surrounded by the three HR2 domains in an antiparallel manner [69].

It was found that there are substantial differences between SARS-CoV and SARS-CoV2 spike proteins. Despite 77.46% of the amino acid sequence in the spike protein of SARS-CoV2 is identical to that of SARS-CoV; however, 243 residues are rich in DCPs mostly in the interacting surface. The RBD of SARS-CoV2 is enriched with DCPs (51 DCPs); about 23% of its residues beside alteration in its sequence location (residues 306-527 of SARS-CoV spike protein while 328-550 in SARS-CoV-2) [66]. Twenty-four amino acid residues of the RBD involved in the interaction with the ACE2 receptors; 16 residues are affinity determining residues. On the other hand, eleven of the 24 residues are DCPs (A430-T433, F460-A471) mainly occurring in the surface loops forming part of the spike protein-ACE2 interface [66, 74, 75]. Five of these DCPs are critical; two of them eliminates two intramolecular H-bondings in SARS-CoV-2 spike protein. While one (N439) of the three DCPs residues (R426=N439, N479=QQ493, Y484=Q498) that forms H-bonding with the ACE2 is absent in the SARS-CoV-2 spike protein-ACE2 interface besides, that the spike side chain is resided away from the interface [66]. Furthermore, one DCP (V404=K417) detected in SARS-CoV-2 spike protein adds an ionic interaction with D30 residue of ACE2 through the K417 residue [66, 74]. This indicates a substantial alteration in the affinity of SARS-CoV2 to this receptor as well as SARS-CoV2 spike protein adapt different conformation at the interaction interface as compared to that of SARS-CoV as well as different interaction with the receptor [66,74,76].

1) The Role Of Human Angiotensine Converting Enzyme2 (hACE2)/ The Cellular Serine Protease TMPRSS2 In SARS-CoV2 Cell Entry, Tissue Tropism And The Expected Clinical Features Of Infection

SARS coronaviruses make use of both its RBD containing spike proteins as well as host cellular soluble or membrane bounded host cells proteases for priming their spike proteins for cell membrane fusion; two critical steps for coronaviruses cell entry and tissue invasion [77]. The spike proteins of SARS-CoV and SARS-CoV2 strains utilizes the same host cell receptor; hACE2 [5,12,78,70,74,77,79-81] with different affinities; 10-20 folds higher affinity of S1 subunit in SARS-CoV2 spike protein which adapt two different conformations as compared to SARS-CoV. The overall shared spike proteins amino acid identity: 76% between the two strains [5,70,77] besides, both have about 89.8% structural homology in their spike proteins S2 subunits explaining their similarity in membrane fusion process mediation. In addition, it is reported that sera obtained from SARS-CoV cured patients can cause cross-neutralization to the cell entry mediated by spike proteins of SARS-CoV2 [12,5,70,77]. However, under the noticed impact of the increased transmission beside the virus potential infectivity some suggest that host cells glycans like sialic acid residue probably be additional factors that may promote cell attachment [77]. This potentiality may explain the greater SARS-CoV2 infection to the upper respiratory tract cells expressing ACE2 receptors relative to SARS-CoV [77] and MERS-CoV [82,83]. In vitro as well as genomic data analysis studies had revealed that SARS-CoV2 virus uses hACE2 expressed in various body tissues for tissue tropism (binding and entry); such as respiratory air ways cells (epithelial and fibroblasts), kidney cells as well as myocardium cells [70,72].

The second essential step in SARS-CoV2 virus entry is priming its spike proteins with the host cell proteases including the lung cells. One of the significantly important targeted host cells porteases that are involved in both SARS-CoV and SARSS-CoV2 priming is the type II transmembrane serine protease TMPRSS2 [9,12, 84,77,85,86]. TMPRSS2 priming process of SARS-CoV2 spike proteins; is like that in case of SARS-CoV spike proteins priming; involves cleavages in the mutibasic arginine rich S1/S2 interface indicating its robustly high cleavability as well as the S2' sits [77]. Accumulating evidence enables one to speculate that TMPRSS2 is a critical for several human pathogenic corona virus strains and that the cleavage sequence may determine their inter-species jump potential as a zoonotic epidemic/pandemic infection to human beings [61, ,77,85,87]. On other hand, despite other cell protease like endosomal cysteine proteases such as cathepsin B/L 9CatB/L) and other cellular proteases may have a secondary/non-essential role in the cell entry of SARS-CoV and SARS-CoV2. However, there are evidences that both viruses probably may use this cellular promoting factor for their spike proteins priming as an additional cell

entry strategy. Thus, TMPRSS2 not CatB/L is the primary priming enzyme critical for both hosts' cell entry and viral infection tissues spread of SARS-CoV and SARSS-CoV2 even though CatB/L activity is dispensable [61, 77, 85,87-89]. In addition, the involvement of pre-cleavage at the S1/S2 interface maintained by furins in the targeted host cells probably contributes the next TMPRSS2 mediated spike protein priming step of cell entry in the infected cells as it is reported for MERS-CoV [90,91]. However, despite the probable independence of SARS-CoV on furin pre-activation of its spike protein for cell entry; remarkably, SARS-CoV-2 relays on such process for its cell entry. This criterion provides this virus strain an opportunity to be less dependent on host cells activation enzymes in addition to gain additional strategy permitting its infection to some types of targeted cells mainly of low TMPRSS2 and/or endososomal cathepsins expression [92]. Two extremely critical aspects should be known about spike protein activation; the life span when it is activated which is finite and the distance of activation event form the host cell membrane that should be proximal; these two aspects are of paramount importance for efficient cell entry of the two SARS corona virus strains [84,77].

In the cleavage site of SARS-CoV spike proteins the presence of R667 and R797 residues are critical in these sites [85,87,93,94] and are conserved in SARS-CoV2 spike protien (R685 and R815). There is a good conservation in amino acid sequences around these two determining residues in the cleavage site; only five DCPs (V663=Q677, S664=T678, T669=V687, S670=A688, Q671=S689) occur in the surrounding of R685 besides insertion of four amino acid residues before it on one hand. On the other hand; very good conservation around the R815 residue; only two DCPs (L792=S810, T795=S813) around this residue occur in proximity [66]. TMPRSS2 inhibitors such as camostat and nafamostat had been found to interfere with SARS-CoV spike protein activation cleavage [61,87,95]. However, it has been recently found that SARS-CoV-2 spike protein is more sensitive to TMPRSS2 inhibitors than SARS-CoV probably due to fore mentioned structural changes in the spike protein cleavage in addition in vitro cell line investigation revealed that cell entry is not limited to the two major host factors TMPRSS2 and ACE2 another factor is also involved [66].

D. Cellular Factors/Expressing Cells Determining SARS-CoV2 Tissue Tropism And The Role Of Interferon Type In Their Expression

ACE2 enzyme as one of the major components of the renin-angiotensin system had gained attention as a fundamental tissue protecting regulator in lung sever injuries both in the sterile and pathological conditions like influenza [96] mediated by angiotensin II through different mechanisms including increase of vascular permeability [88,97]. ACE2 expression has of interferon-stimulated gene especially in the epithelial linings of human body organs that is up regulated upon interferon release as a host tissues protective inflammatory mechanism during its antiviral defense; however, it could be exploited by some viruses [30]. Three crucial lessons have been learned after the last two decades viral epidemics; first beside the immune defense an accompanying physiological responses and factors evolves to enhance the host ability to tolerate tissue damage especially after equivalent pathogens impacts [96-99]. Second, ACE2 is one of the significantly important early tissue tolerance factors during acute respiratory tissue infections including viral one [99]. Three; some viruse infections like H5N1 influenza infection increases ACE2 expression while others like SARS-CoV causes down regulation in the ACE2 expression [88,100]. Others argued that the publicly conformed database revealed that SARS-CoV and MERS-CoV infections also stimulate the expression of ACE2 in the epithelial cells of upper airways [96,97,101,102]. However, it is required to specify whether SARS-CoV2 infection and accompanied inflammatory response increases or decreases ACE2 expression.

Interestingly, both of SARS-CoV and SARS-CoV2 makes use of such body tolerance protective mechanism; ACE2 expression as expansion cellular entry and one of its hijacking mechanism to tissue and cells biochemical ordinary events [43]. This pathogenic behavior of these two coronaviruses of targeting the same receptor subset; ACE2 in the target cells [5,75-77] is not encountered with previous strain HCoV-OC43, that binds to the two restriction factors IFITM2 and IFITM3 [43, 103] which may add an additional challenge to the host defenses and therapeutic intervention. Therefore, to understand the fundamental mechanism of SARS-CoV2 tissue tropism and thereby, targeted cell types, targeted organs and the expected clinical manifestations in the vulnerable population of infection requires a comprehensive characterization to the cell types expressing one or more SARS-CoV2 binding/entry promoting factors. These objectives require first; identifying the host cell subsets targeted by SARS-CoV2 like $ACE2^{+}$ cells which are of great risk of infection as well as $ACE2^{+}$, $TMPRSS2^{+}$cells of definite direct infection in various body tissues and organs. Second; the role of host defense inflammatory mediator; interferon; in regulating ACE2 and TMPRSS2 expression in these tissues [43]. Ongoing studies and investigations are devoted to specifying whether both of ACE2 and TMPRSS2 or any of them on host cell is required to be targeted by SARS-CoV2 or even soluble proteases activation of SARS-CoV-2 spike proteins are required to make the invasion of cells expressing only ACE2 on their membrane accessible [79, 103]. Recently, similar SARS-CoV targeted subsets of cells in the lung are proposed for SARS-CoV2 mainly those expressing ACE2 like pneumocytes and macrophages besides the cells of extra-pulmonary tissues where SARS-CoV also infects despite their substantial difference in spike protein affinity [77, 105-107]. However, the modest expression of ACE2 receptor in the upper respiratory tract cells speculate the limited SARS-CoV transmissibility [77,106,107]. In this context, Ziegler and his co-workers have utilized an up-to-date virtual single-cell RNA-seq analysis technique for analysis of datasets obtained from humans during health and disease conditions for identifying cellular targets of SARS-CoV2 occur at barrier tissues depending on ACE2 and TMPRSS2 expression [43,108,109]. Their meta- analysis speculates that Type II pneumocytes in the lung, nasal mucosa goblet secretory cells, constituting a rare subset of the epithelial

tissue in addition to the gut ileal absorptive enterocytes are co-expressing ACE2 and TMPRSS2 ($ACE2^+$, $TMPRSS2^+$ cells) [43] however, several other studies are in high in accordance with such tissue subset rich co-expression [110-113]. These cells are probably the primary targets for SARS-CoV2 infection however, other subsets of respiratory epithelium cells like pneumocytes type I mostly expressing ACE2 individually which are also could be targeted by the same virus. Despite the minute abundance as compared to type II pneumocyte; TMPRSS2 expression is also detected in club cells, ciliated epithelial cells, and type I pneumocytes [43]. Another published HCA Lung Biological Network study had identified ACE2 and TMPRSS2 rich co-expression in the nasal mucosa goblet and ciliated cells [114].

1) Upper Airways, Lung And Gut Epithelial Cells Expression Of Host Coronavirus Entry Promoting Factors; ACE2 And TMPRSS2

The primary coronaviruses exposure sites located in the upper airways of human beings are the inferior turbinate and ethmoid sinus mucosa however, a minority cells in these tissues; 1.3% was identified expressing ACE2 mainly the secretory cells providing earliest location for infection establishment to these viruses. Some of the apical epithelial cells (1% of them) then, to a lesser extent, ciliated cells are identified to be enriched with ACE2 [43]. Furthermore, with in the whole upper airway mucosa cells secretory cells including goblet cells are found to be of significantly high ACE2 and TMPRSS2 expression (4% of them express ACE2, 28% of them express TMPRSS2) on one hand. On the other hand, the vast majority of TMPRSS2 and ACE2 co-expressing mucosa cells are the secretory one encompassing 0.3% of the mucosa as well as 1.6% of goblet cells [43, 114]. Secretory cells in the Inferior turbinate; namely goblet secretory cells taken from healthy and allergically inflamed chronic respiratory disease donors with chronic rhinosinusitis have been identified to have specific expression on ACE2 4.7-9.8% in different subsets while 1.9%-4% ACE2 and TMPRSS2 co-expression in another one [115]. Interestingly, no ACE2 expressing cells was detected in polyp tissue cells while few one found in the ethmoid sinus tissue of chronic rhinosinusitis patients without nasal polyps. These cells have been found to have rich IFN-dominated gene signature particularly in the inferior turbinate secretory epithelial cells [43].

In the lung tissue beside the ciliated cells; type II pneumocytes are identified to have the major expression of ACE2 and TMPRSS2; 1.4% expressing ACE2, 34.2% expressing TMPRSS2 and 0.8% co-expressing both. However, other pattern of expression is identified in the ciliated cells; 7% expressing ACE2, 24.6% expressing TMPRSS2 and 5.3% are co-expressing both. However, previous infections like tuberculosis in these cases the co-expression of ACE2 and TMPRSS2 is escalated to 22% of the type II pneumocytes and 9.7% of type I pneumocytes. The availability of such escalated ratios of cells in the lower airways provides an additional evidence to the role of inflammation related interferon-promotion of ACE2 up-regulation in these subsets of cells [43]. However, a cohort study in pediatric patients have identified virus stimulated up-regulation of ACE2 and IL-13 stimulated up-regulation of TMPRSS2 which led to the speculation that the predisposing allergic conditions or co-infection can up-grade these two hosts SARS-CoV2 promoting factor in addition to the presence of Furin enriched olfactory epithelial gland cells [43, 116]. Moreover, both of interferon and influenza virus infection have an ACE2 expression stimulate effect the nasal epithelia and lung tissue in humans on one hand; on the other hand, treatment of upper airway basal cells with IFN-a have promoted ACE2 expression. Thus, human inflammatory response within the infected tissue or even due to previous or co-virus infections promotes the ability of SARS-CoV and SARS-CoV-2 target these tissues in addition to develop an additional adjacent cellular target in the upper airway epithelial cells [43]. It has also identified that 29.7% the absorptive enterocytes taken from the terminal ilium parts of pediatric donors express ACE2 while 6.5% of the ilium epithelial cells co-express ACE2 andTMPRSS2. This finding beside the detection of SARS-CoV2 viral RNA in rectal swaps after negative nasopharyngeal tests in pediatrics strength the suggestion that this virus has GIT mucosa tropism beside explanation to some recorded intestinal symptoms like diarrhea and vomiting [43,117].

Very recently, an in vitro study used cell lines of various ACE2 and/or TMPRSS2 extent of expressions have revealed that there is no strong correlation between the level of ACE2 abundance and the cellular susceptibility to SARS-CoV2 and to a lesser extent to SARS-CoV. This study also showed that SARS-CoV2 has a relatively ACE2 independent entrance to the ACE2 expressing host cells in the tested cell lines despite the use of anti-ACE2 antibodies on one hand; on the other hand, cell of no ACE2 expression does not support the entrance of SARS-CoV while a limited entrance was encountered with SARS-CoV-2 [66]. In addition, the greater anti-ACE antibody activity against SARS-CoV as compared to SARS-CoV2 in cell lines of abundantly expressing ACE2 may indicate the higher binding affinity of SARS-CoV2 supported by other studies to the ACE2 receptor which probably be so strong to be antagonized with such antibodies [66,70,81]. However, the MERS-CoV receptor; DPP4 directed antibodies have no interference with the with SARS-CoV or SARS-CoV-2 infection [9,19,66]. Other cell lines of like colorectal cancer cell line CL14 of lower ACE2 levels and TMPRSS2 expressions support SARS-CoV2 infection. This means that extent/abundance of ACE2 expression are not sufficient determinant to the cellular entrance of SARS-CoV2 and to a lesser extent SARS-CoV; hence they may not really have a significant impact on host tissues susceptibility SARS-CoV-2 infection. Moreover, this study suggests other cellular promoting factors besides the presence/degree of expression of ACE2 levels and TMPRSS2; that may also determine the cellular susceptibility to SARS-CoV-2 infection, tissue tropism and drug sensitivity profiles [66] like ACE2 higher affinity. This suggestion contrasts with previous studies dedicating a central role to ACE2 in SARS-CoV2 tropism [118-120]. Finally, this study determined significantly important structural/biological behavior differences have been identified between SARS-CoV2 and SARS-CoV

regarding cellular susceptibility to infection, tissue tropism and drug sensitivity profiles suggesting that only drug testing is the useful approach for identifying a therapeutically useful candidate for SARS-CoV2 infection [66].

Regarding the influence of interferons on ACE2 expression, it has been found that only IFN-α2 and IFN-γ have time and concentration dependent stimulation of ACE2 expression in the upper airway epithelial cells including the nasal mucosa; however, IFN-α2 has a significantly greater stimulation including IFITM1 induction [43,121]. While, IFN-γ showed more robust up regulation of GBP5, a GTPase-like protein [43] which are believed to be inhibitors of the furin-mediated protease activity so limiting viral spike protein priming; thus, they may be considered as viral entry restriction factors [121]. Asthma as predisposing factor may include interferon release has a variable effect on ACE2 expression ranged from strong to weak induction or even minimum changes. Furthermore, treatment of the primary bronchial cells with either of type I or type II IFN showed more than five folds up-regulation of ACE2 in these cells [43]. Ultimately, type I interferons and to a lesser extent type II interferons can up-regulate ACE2 expression in the respiratory system mucosa; IFN-α, and to a lesser extent IFN-β or IFN-γ can stimulate ACE2 expression in the nasal epithelial cells as well as basal cells since they have the highest IFN-α-induced gene signature [43,122,123]. Similarly, ACE2 in primary bronchial cells and keratinocytes is up regulated by type I interferons [124].

Regarding the viral predisposing infection/co-infection influence on the expression of ACE2 in the respiratory airways; influenza virus is well known interferon pathway inducer hence its infection causes elevation in the ACE2 expression in the nasal epithelium goblet secretory cells [43, 125]. Others claims that these goblet cells as well as squamous cells are even when not directly infected with the influenza virus, they by stander co-express ACE2 and TMPRSS2 during the infection [43]. Unfortunately, coronaviruses and other viruses have acquired an evolutionary feature that can exploit the tissue destruction tolerant interferon pathway consequences for cell entry and thereby establishment of their infection [102,103,126]. Beside risk factors like infection, age, gender, and co-morbidities dependence in addition to the stage of infection; cell subsets and infecting coronavirus stain; judging that type I interferons are of protecting or harmful influence the infected host tissue is still in query [11,101,127,128]. Currently, there are growing evidence that at least interferons assume that they have opposite dual effects; the first through enhancing SARS-CoV2 entry to the targeted host cell subsets while the second through induction of tissue protecting host response however, both are mediated through stimulating ACE2 expression within the infected tissue especially in the upper airways. This dual opposite roles of interferons in case of SARS-CoV2 and SARS-CoV infection is needed to be undoubtedly discriminated for better therapeutic intervention taking in consideration establishment of a good balance between host restriction, tissue tolerance, and viral enhancement mechanisms [43].

Probably not less than 10 coronavirus proteins have roles interferon activity counteraction including p6, nsp3, nsp14, nsp1, nsp15, N and M [129,130,66]. Recently, an Insilco study have revealed structural variation in the structure of these proteins (DCPs) including p6 and the papain-like protease (nsp3) which are DCPs rich, nsp7 and nsp16 which are depleted in DCPs while the last five proteins (nsp14, nsp1, nsp15, N and M) contains intermediate proportions of DCPs. However, the tenth protein available in SARS-CoV; p3b is not available in SARS-CoV-2 [66]. These structural changes especially those in p6 and the papain-like protease may affect the SARS-CoV2 interferon inhibition capability [66] as well as explains the interferon inhibition variation between SARS-CoV and SARS-CoV-2 [129]

II. CONCLUSION

SARS-CoV2 binding receptor had extra-pulmonary/respiratory passages excessive expression, especially in the GIT. This virus novel strain also has some structural as well as genetic material variation as compared to SARS-CoV1 especially with in the spike protein RBD-ACE2 binding interface that can be targeted for drug design. In addition, the host factors especially the priming enzymes like the serine proteases including TMPRSS2 as well as furins could have an implication in the combating of its infection. Finally, previous viral infections such as influenza virus infection may provide an additional entry approtunity to SARS-CoV2 as it increases the interferon dependent ACE2 expression in the patient air way hence enhancing this virus cell entry as well as may explain the high infection acquisition/severity within the winter.

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