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Review Article

Molecular Characterization 2019 Novel Coronavirus (COVID-19): A Review of the Current Literature

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Abstract

December 2019 was the initiation of a major challenge for the global health community. World attention shifted to novel beta coronavirus disease 2019 (COVID-2019) that caused the severe acute respiratory syndrome. Commonly, infected droplets transmitted by inhalation among people lead to disease. Detection of the virus in respiratory secretions by special molecular tests and computerized tomographic chest scan is usually possible. The role of a wide range of therapeutic agents is investigated to help 2019-nCoV patients. Given the extensive research in this area, it is necessary to perform a literature to review the currently published paper results. We focused to gather related articles about the molecular pathology of 2019-nCoV. Based on our results, suggested that interferon pretreatment and immunomodulatory agents to decline the cytokine storm and can be helpful in fighting COVID-19, this is while that community-wide vaccination undoubtedly can develops immunity and *definitely* provides protection.

Keywords: Coronavirus; 2019-n-CoV; COVID-19; Molecular Pathology; Treatment; Vaccine

Introduction

Nowadays, unfortunately all of the world lives was affected by the 2019 novel coronavirus (2019-nCoV) which was originated in China in December 2019 [1]. Main and less clinical features are ranging from fever, dry cough, tiredness to aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discolouration of fingers or toes. Importantly, serious symptoms including difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement are considered dangerous. Chest CT patterns in COVID-19 divided into three main phenotypes with different characteristics [2,3]. The median course for this disease is almost 10 days. The people who are suffering from serious underlying medical conditions and chronic diseases, such as diabetes, hepatitis B, asthma, HIV, older adult, long-term use of hormones or immunosuppressants, and decreased immune function have been considered vulnerable ones [4]. Based on single-cell RNA sequencing and immune histochemical staining, ACE2 is expressed in a number of human organs such as kidney cells as well as intestines, the probability of kidney impairment increased and elevated plasma creatinine levels in pa-

tients. Hence, the plasma creatinine levels in 2019-nCoV patients might be a sign of disease progression [5]. According to another study on the neuroinvasive potential of 2019-nCoV, virus infection would probably attack the nervous system including neurological disorders. Hence, awareness of these conditions significantly helps for the prevention and treatment of the 2019-nCoV [6].

Preventing the spread of 2019-nCoV is the most important and urgent task. Early detection and isolation are essential to decline this exposure. Taking throat swabs is significant in COVID-19 screening. RT-PCR, real-time reverse transcription PCR (rRT-PCR), reverse transcription loop-mediated isothermal amplification, as well as real-time RT-LAMP are practical for COVID-19 diagnostic. There are three real time RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), S, and N genes of 2019-nCoV [7].

The novel virus especially British, South African COVID variants due to the high rate of transmission and lacking proper and specific treatment becomes a real disaster these days. This article tends to give invaluable information about the molecular pathology of this new virus.

At present, we must bear in mind that specific treatment for COVID-19 is related to identification on the basis of 2019-nCoV replication, structure, and pathogenicity. Since identifying the specific molecular details of the virus is helpful in achieving treatment goals, all on the efforts and further research must be coordinated and are imperative for identifying appropriate therapeutic targets for COVID-19. Up to now (10 April of 2021), 5273 studies were registered in https://www.clinicaltrials.gov/ct2/covid_view and the speed of the investigation are extremely unbelievable.

Molecular characterization COVID-19

Origin and structure

2019-nCoV is an enveloped positive-sense RNA virus that belongs to the subfamily Coronavirinae in the Coronaviridae of the order Nidovirales and β coronavirus family. It was identified possessing >95% homology with bat coronavirus and > 70% similarity in gene sequence and behavior pattern with SARS-CoV [8]. Their name was attributed because of their crown-like appearance due to spike (S) under the electron microscope. Scientists have already suggested that 2019-nCoV originally came from bats, but probably transmitted to humans by pangolin with 99% sequence similarity [9]. The Human 2019-nCoV virus could not come from pangolins directly because pangolins did not have the RRAR motif, a unique peptide (PRRA) insertion which may be involved in the proteolytic cleavage of the S protein by cellular proteases [10]. Four amino acid insertions (PRRA) create a new poly base cleavage site (RRAR motif) for the 2019-nCoV S. The homology modeling revealed some molecular and structural differences between the viruses, for example, the presence of two beta-sheets on the 2019-nCoV in contrast with the SARS-COV structure. Meanwhile, the analysis depicts that the nucleocapsid (N) and the S glycoprotein have some sites under positive pressure [11]. The virus has six ORFs (Open reading frame), the first ORF (ORF 1a/b), in the 5' terminus, is the largest ORF and produces polypeptide 1a (pp1a) which is processed into RNA-dependent RNA polymerase (RdRP). Selective pressure caused mutations in Open Reading Frame 1ab (ORF1ab) on different amino acid residues in positions 501 (position 321 of the nsp2 protein), 723 (position 543 of the nsp2 protein) and 1001 (position 192 of the nsp3 protein) which directly impacts on the virus ability to infect human host. ORF 1ab in position 501 has an apolar amino acid in the Bat SARS-like coronavirus while the SARS and 2019-nCoV have a polar amino acid [21]. The ribosome frameshift in ORF1a stop codon allows translation of ORF1b continues and a large polypeptide (pp1ab) is cleaved into 16 nsps. Viral proteases nsp3 and nsp5 are responsible for the proteolytic cleavage that bear a papain-like protease (PLpro) and 3C-like protease (3CLpro), respectively [13].

The other ORFs near 3'-terminus encodes the structural parts of the virus including S, membrane (M), envelope (E), and N proteins. S protein produces the S of the virus, M protein is responsible for binding to the neucleocapsid and shapes the virion and promotes membrane curvature. E protein involves in pathogenesis of viruses as well as viruses assembly and release process. The N protein has two domains that bind to the virus RNA genome and are the antagonist of Interferon (IFN) as well as a repressor of RNA interference in virus [14]. The data revealed that the N protein recruitment to replication-transcription complex (RTC) as a critical step for virus infection via nsp3 binding and synthesis of RNA virus [15].

Furthermore, 3'-5'-deoxyribonuclease of nsp14 which is unique to COVs provides proof reading function of RTC; hence, four structural proteins for virion assembly are essential. It is also quite evi-

dent that the novel 2019-nCOV has a short protein with four helices found within ORF3b, which has no homology to existing SARS-CoVs proteins [16]. It is noteworthy that although ORF3b is not necessarily vital for viral replication, it may have a role in pathogenicity IFN-β expression suppression. Different ORF3b with varied IFN antagonist activities are responsible for the protein's nuclear localization [17].

As some scientists ascertain, 2019-nCOV genome evolves after entering the host cells, which affect its virulence, transmissibility, and infectivity; thus, it is of great importance to boosting the supervision of viral evolution in the population. Most of the 2019-nCoV and SARS-CoV virus proteins are highly homologous (95%–100%), indicating the evolutionary similarity. However, two proteins (ORF8 and ORF10) in 2019-nCoV have no homologous proteins in SARS-CoV and must be analyzed. N protein as the most frequent one shares ~90% amino acid identity and does not provide immunity against infection, but the antibodies have cross-reactivity with N protein of SARS-CoV, which would allow a serum-based assay to identify the asymptomatic 2019-nCoV infected-cases. In addition, S stalk S2 in 2019-nCoV shares 99% identity with similar viruses. Thus, the broad-spectrum antiviral peptides against them must be examined clinically [18].

Spike protein structure and function in pathogenesis

S glycoprotein has a large ectodomain, which consists of a receptor-binding unit S1 and a membrane-fusion unit S2a, and a single-pass transmembrane anchor, as well as a short C-terminal intracellular tail . The S1 subunit includes a signal peptide, followed by the receptor-binding domain (RBD) and N-terminal domain (NTD). The S2 subunit contains conserved fusion peptide (FP), heptad repeat (HR) 1 and 2, transmembrane domain (TM), and a cytoplasmic domain (CP). Because some 2019-nCoV strains have no stretch of deletions in the S RBD can use human ACE2 as a cellular entry receptor [17]. The fusion of SARS-CoV is similar to HIV-1. S1 shows the most variability in its residues when comparing it between SARS-CoV and 2019-nCoV. Due to the fact that S1 is an essential target of vaccines, SARS-CoV treating vaccines cannot be successful against 2019-nCoV when targeting S1 [19]. S gene constitutes two subunits including S1 and S2. S1 is responsible for defining the host range of viruses and the cellular tropism. S2 is responsible for virus-cell fusion. A clove-shaped S consist of three S1 heads and a trimeric S2 stalk can form S glycoprotein. Viruses enter to a host cell by S1, and S2 fuses the host cell and viral membranes. Some specific cleavage at specific sites is essential for viral entry and releases a viral genome into the cytoplasm. For example, some proteases such as cathepsin L, trypsin, elastase, and TMPRSS2 have been shown to cleave S protein. In addition, 2019-nCOV has an additional furin-like protease cleavage site as well, which is located in N-terminus to the S1/S2 and S2′ site that is identical. however, it could be suggested that these proteases inhibitors may be valuable in suppressing 2019-nCOV infections [20]. Therefore, S glycoprotein can be an important target for vaccine development, therapeutic antibodies, and diagnostics. The RBD of the S1 subunit of 2019-nCOV S protein, hide, or display two states that are referred to as the "down" and "up" conformations based on receptor-inaccessible state and up corresponds to the receptor-accessible state. MSC that are known to have immunomodulatory effects can be used to attenuate the cytokine storm (secretion of a large number of inflammatory factors: IL, IFN, C-X-C motif chemokine (CXCL) and so on,) arisen from virus infection and eventually to cure 2019-nCoV patients (28).One of the three RBDs which is accessible is common [21].

2019-nCoV will cause ACE2 but not ACE receptor downregulation, through binding of S-protein to ACE2, which activates the entrance of virus and viral replication with severe lung injury (33). ACE2 is the receptor that 2019-nCoV applies to infect lung cells; and these lung AT2 cells are susceptible to viral infection. In 2019-nCoV, S gene codes S protein that binds to ACE2 which is needed for the infection to be initiated. A fragment consisting of 193 amino acids has been reported to be more efficient in binding to ACE2 rather than its unmutated form. This fragment in S protein consists of 21 mutations, has a potential role in the human host adaptation. There are three peptides named NSP1, NSP3, and NSP15 which have an unclear role but essential in the 2019-nCoV outbreak. NSP1 will help in the gene expression of virus and evading host immune system response. NSP3 will cooperate with cleavages, the replication of the virus, and offending innate immunity. NSP15 is an endoribonuclease that is specific for uridylate. NSP1 and NSP3 are associated with passive status after the infection. Three peptides (NSP1, NSP3, and NSP15) and S gene are associated with the 2019-nCoV epidemic and these are satisfying for further investigations [22,23].

ACE2/RBD complex

Human ACE2 catalyzes the conversion of angiotensin I to the 1-9 or the conversion of angiotensin II to 1-7 and has seven beta-sheets in the backbone of the RBD. There are three loops and two B-sheets, which are involved in the interaction between ACE2 and RBD. Among 16 amino acid residues that are in contact with ACE2 in SARS-CoV RBD, eight residues are conserved in 2019-nCoV, which plays a pivotal role in binding affinity. There is also a hydrophobic L472 residue, which is essential for ACE2/RBD interaction and is located in a loop via a disulfide bond. The amino acid sequence in this loop which is CTPPALNC is replaced into CNGVEGFNC in 2019-nCOV and contains an extra amino acid residue and completely different amino acid composition. The substitution of two proline residues with two glycine residues reduces the stiffness of the structure and makes it more flexible. F486 in the novel loop, which is more flexible, can strongly, transpires into the hydrophobic pocket in ACE2, which is composed of F28, L79, Y83, and L97 [24]. Altogether, 2019-nCOV has much more binding affinity to ACE2 via its S glycoprotein. There are 23 glycosylation sites on the S protein, of which two sites are in RBD, one of them is Asn 343 in 2019-nCOV, Asn330 in SARS-COV, which is highly conserved. Interestingly, the other glycosylation site, N357 in SARS-COV has been undertaken a substitution of T by an in +2 position, which is not speculated to affect binding affinity. Apparently, finding a way to suppress ACE2/RBD interaction is the best way to suppress virus infection, which can be achieved by small molecules inhibitors or antibodies [25]. It is noticeable that because a number of ACE2 variants could reduce the binding affinity between ACE2 and S-protein in SARS-CoVs, the varied expression level and pattern of human ACE2 might be important for the susceptibility, symptoms, and spreading of 2019-nCoV infection. In compliance with this notion, it is suggested with a study on single-cell RNA-seq analysis that the Asian patients had a much higher ACE2 expression cell ratio than white and African-Americans; moreover, the ACE2 expression cells are a very small part of cells in lung tissues [26].

It is suggested that the antibodies, which target the identified linear B-cell epitopes in the S2 subunit, might neutralize both SARS-CoV and 2019-nCOV. In addition, it is noticeable that the discontinuous B-cell epitopes which were identical in SARS-CoV and 2019-nCOV might not be able to bind to the same regions in 2019-nCOV S protein. 2019-nCoV and SARS-COV can bind to ACE2; whereas, MERS-COV bind to DPP4 [27].

IFN-stimulated genes restrict virus replication steps. It is reported that GILT (gamma-IFN-inducible lysosomal thiol reductase) which is a lysosomal associated IFN-stimulating gene, may suppress the glycoprotein-mediated entry of SARS, MERS and Ebola viruses. GILT expression in lung epithelial cells, as well as fibroblasts, can be induced by IFN type II; also, the induction of GILTS expression results in the reduction of Cathepsin L activity, which is needed for RNA virus entry. Furthermore, it is investigated that losing thiol reductase activity via devastated N-linked glycosylation, which is essential for GILT lysosomal localization, strongly is influenced by GILT restriction of virus entry. Therefore, GILT which is a novel antiviral agent against RNA viruses may have a critical role in immune control.

In a recent study, it is revealed that Mesenchymal Stem cell (MSC) injection may be effective in 2019-nCOV treatment via increasing the peripheral lymphocytes and interleukin (IL)-10 as well as depleting the tumor necrosis factor (TNF) α, NK cells and C-reactive protein, which is an evidence for the alleviation of the virus infection [28]. Given that the immunity-related organs such as bone marrow, spleen, lymph nodes, thymus, macrophages and immune cells (T-cells and B-cells) are $ACE2^{-}$, it is assured that immunological therapy may be implemented as a potential treatment for 2019-nCOV.

CLpro and PLpro

3CLpro and PLpro are two proteases that process translation and are important in the replication and packaging of the viruses. PLpro deubiquitylate host cell proteins such as IFN regulatory factor 3 (IRF3) as well as to inactivate the pathway for nuclear factor k-light chain- enhancer of activated B cells (NF-kB) that suppress immune in the cells host. Recently, Simmons and co-workers developed a class of vinyl sulfone small molecules that potentially target 2019-nCoV entry and able to inhibit virus replication [29]. It is frequently asserted that the previous SARS enzyme inhibitors can be considered for 2019-nCOV treatment because of highly conserved regions in SARS and 2019-nCOV genomes. Among all virus 3CL-pro which cleaves PP1AB proteins and is essential for viral replication, maybe a potential drug target; given that the PP1AB cleavage site sequences, as well as all 3CL protease sequences between SARS and 2019-nCOV, has been 100% conserved. Therefore, based on the 3CL-pro simulated molecular model of 2019-nCOV,

the available drug agents have been identified, which may be used to fight 2019-nCOV inhibition. Finally, it is recommended that Velpatasavir as well as Epclusa and Harvoni, could be the potential drugs due to their inhibitory activity on 2019-nCOV enzymes [30]. Among more than one dozen proteins, which encodes by a coronavirus and some shows necessity in the entrance of virus and its replication, PLpro, 3CLpro and S-protein are investigated more than others. PLpro processes the polypeptide of the virus into proteins with functionality, but it can dampen the anti-viral response by the host as a deubiquitinating enzyme by stealing the ubiquitin system. SARS-3CLpro is crucial for the life cycle of the virus and is a cysteine protease [31].

Treatment via molecular function and immune response

2019-nCoV infectivity can be described as it binds ACE2 receptors by a higher affinity that is comparable with influenza patients and is divergent from SARS-COV. ACE2 is a type 1 membrane protein, expressed in the lung, heart, kidney, and intestine, and down-regulation of it will cause cardiovascular-pulmonary diseases. ACE2 will cleave angiotensin 1 to Ag-(1-9) which will then process to Ag-(1-7). Also, Ag-(1-7) be produced from the direct effect of ACE2 on AgII. AVE 2is a chaperon for membrane trafficking of amino acid transporters named SLC6A19 that are responsible for the intake of neutral amino acids into intestinal cells. 2019-nCoV enters the cells via ACE2 receptor and primes S-protein by TMPRSS2 (a serine protease). One approach for entry blockage of 2019-nCoV would be TMPRSS2 inhibitor that may become a treatment choice. Antibodies targeting ACE2 can block viral replication in Vero-E6 cells. Among antiviral therapies, lopinavir and/or ritonavir protease inhibitor that previously were used to treat HIV infection showed efficient for some COVID-19 patients, host cell factors ACE2 and TMPRSS2 and can be blocked by a clinically proven protease inhibitor [32]. An adaptor-associated kinase (AAK1) is an endocytosis regulator and the disruption of it might prevent the virus passage and the assembly of particles intracellularly [33]. Baricitinib is defined as an inhibitor of the numb-associated kinase (NAK), which shows a high affinity for AAK1. Baricitinib, Ruxolitinib, and Fedratinib are the potential inhibitors of JAK-STAT signaling and they are possibly effective in 2019-nCoV due to their effect on the stage an increased level of cytokines [34]. The exact in vivo effect of Aflavin on RdRp targeting needed to confirm future researches (44). Vinylsulfone protease inhibitors potentially prevent the 2019-nCoV entry by influencing on 3CLpro and PLpro [29]. Additionally, the therapeutic options for 2019-nCoV would be vaccines targeting S protein (against S1 subunit); inhibition of the activity of TMPRSS2, and blockage of the ACE2 receptor.

Infection-related biomarkers and inflammatory cytokines are increased. The number of T cells (helper, suppressor, and regulatory) is decreased. Higher serum levels of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6) and chemokines (IL-8) are reported in severe COVID-19 patients in comparison with mild ones, similar to the results in SARS and MERS. It was declared that higher expression of cytokines and chemokines in immunity and pathogenesis during virus infections. The consumption of CD4+ and CD8+ T cells and the production of the cytokine storm lead to inflammatory responses and damaging [19]. 2019-nCoV will induce higher levels of IL-6 for nearly two weeks of post disease onset. ADAM-17, SARS-CoV single-strand RNA, DUSP1, and p38 MAPK that are related to the IL6 pathway proposed for having the potency to be therapeutic targets [35].

Inflammatory cytokines including IL2, IL7, IL10, MCP1, IP10, MIP1A, GCSF, and TNFα increased during disease progression. 2019-nCoV is known for its dangerous inflammatory storm, which is as a result of activation of cellular and natural immunity and also Toll-like receptors and killer T-lymphocyte activation. Activation of T-cells will lead to destroying the infected cells and finally T cell depletion; this is the reason for releasing DAMPs (for example fragments of DNA, B1 high mobility group protein). Then inflammatory signals will further be activated but due to the T-cell depletion, T-cells cannot control the infection. As a result, inflammatory signaling pathways will be more activated and finally, reactions of secondary inflammation will initiate, and inflammatory cytokines in large numbers will be released including TNF, IL-6, IL-18, and others which will cause at the end to damage to multiple organs [30]. Antibody-dependent enhancement or ADE prevents the management of inflammation and as a result, the symptoms of 2019-nCoV will arise [36]. The immunomodulatory agent's usages including Ulinastatin, for cytokine storm treatment, and anti-inflammatory properties (IL-6inhibition), called more attention. chloroquine and its derivative hydroxychloroquine can inhibit MHCII expression, APC, and immune activation (reducing CD154 expression by T cells) via Toll-like receptor signaling, cGAS stimulation of interferon genes and reduce the production of various pro-inflammatory cytokines, such as IL-1, IL-6, interferon-α and TNF. Tocilizumab is a

monoclonal antibody that blocked IL-6 and reduced fever and lung lesion opacity. In addition, the consumption of corticosteroids in conjunction with other drugs are appeals to many more debates for 2019-nCoV treatment.

According to a report on the implementation of convalescent plasma or immunoglobulins, which is highly tested for the Influenza virus and MERS-COV, it is evident that convalescent plasma from 2019-nCOV recovered patients may be considered as a potential treatment strategy. A novel serum antibody (IgM and IgG) specific for coronavirus as a detection procedure has become marketed with a 100% positive rate to replace swab sampling from nasopharynx but it needs clinical validation [37]. 2019-nCoV possess strategies for the delay in IFN production, which leads to severe disease. Severe cases show higher plasma levels of IL2, 6, 7, 10, GSCF, IP10, MLP1A, MCP1, and TNFα, as a matter of fact, the release of cytokines is critical for the progression of the disease. Due to the induced apoptosis by 2019-nCoV in lymphocytes, patients show lymphopenia. Pre-inflammatory cytokines and immune pathways and affected by 2019-nCoV. Analysis of the KEGG pathway showed that lymphopenia produced due to the induction of apoptosis, lymphocytes, and the P53 signaling pathway.

A wide ranges drugs were suggested for COVID-19 treatment such as, Dexamethasone, Antiviral, interferon-α inhalation, lopinavir/ritonavir, arbidol, glucocorticoids, intravenous immunoglobulin, extracorporeal membrane oxygenation (ECMO), continuous renal-replacement therapy (CRRT). Meanwhile, in the last version were announced in https://www.covid19treatmentguidelines.nih.gov/whats-new/, it was declared that dexamethasone, **remdesivir,** tocilizumab, bamlanivimab and etesevimab can be effective. It is needless to say that zinc, vitamin D and vitamin C are helpful to treat also [38,39].

Vaccine

A number of various vaccine strategies were investigated including inactivated or live-attenuated viruses, viral vector-based vaccines, subunit vaccines, recombinant proteins, and DNA vaccines [14]. In a study was done using a molecular docking approach it is suggested that novel ACE2 inhibitors such as N-(2-aminoethyl)-1 Aziridineethanamine, could suppress RBD cell fusion via binding to the catalytic center of ACE2 and subsequently, impact on the ACE2/RBD interaction via changing RBD binding site conformation [21]. Although, it is demonstrated that because of differences in the RBD structure of SARS-COV and 2019-nCOV, the present antibodies against SARS-COV may not be effective in 2019-nCOV infection. Some of the SARS-CoV-specific neutralizing antibodies (e.g. m396, CR3014) target the ACE2 binding site failed to bind to S protein, implying that RBD difference of SARS-CoV and 2019-nCoV has a critical impact for the neutralizing antibodies cross-reactivity [40]. However, it is illustrated that CR3022, interact with 2019-nCOV RBD with high affinity. RAS cascade is the target place of 2019-nCoV due to the application of ACE2 as the entry receptor by the virus, and it will cause pulmonary damage. Chymase is another enzyme rather than ACE which can convert AngII. Taken together, There are several treatment options that may be helpful for 2019-nCoV patients as follows, an antimalarial chloroquine and hydroxychloroquine, antivirals, passive immunization therapy, IFNs, antibacterial antibiotics (moxifloxacin, ceftriaxone, azithromycin), Glucocorticoid, oxygen inhalation, noninvasive ventilation, transient hemostatic medication for hemoptysis, nutritional support and maintaining fluids, electrolyte, and intestinal microbiological modulator balances.

WHO approved three types COVID-19 vaccine named Pfizer-BioNTech, Moderna, Johnson and Johnson's Janssen. Besides, there are twelve vaccine which were under investigation, which are affordable as well. Some advanced vaccine producing technologies such as viral vectors, lead to a substantial increase in different biopharmaceutical proteins. It is evident that a great number of plant-produced recombinant antigens as well as monoclonal antibodies have a great effect on human infectious disorders. Thus, the identification of potential epitopes as well as the production of subunit vaccines expressing immunogenic region or chimeric proteins in plant-based biopharmaceutical vaccines against 2019-nCOV would be effective. The potential vaccine candidates are based on the nucleoside modified mNRA, recombinant ChAdOx1 adenoviral vector encoding the spike protein antigen of the SARS-CoV-2, mNRA-based vaccine encapsulated in lipid nanoparticle (LNP), recombinant replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) spike protein, recombinant novel coronavirus vaccine (adenovirus type 5 vector) peptide antigen, recombinant protein subunit RBD in S protein of 2019-nCOV [41].

CRISPR/Cas13d system by using the guide RNAs (gRNAs) that concomitantly target ORF1ab and S, can disrupt the virus function, but it is noteworthy that the safety and efficacy must be considered.

Discussion and Conclusion

In this review, we tend to summarize all the potential molecular knowledge and targets of COVID-19 infection The incubation duration of 2019-nCoV was reported 3 to 6 days [32] with current mortality nearly 3.4%. The main antigen of 2019-nCoV is glycoprotein S antigen can be applied for typing; meanwhile, N can be applied for 2019-nCoV diagnostic applications [42]. Today, no specific drug exists for 2019-nCoV. According to respond to the outbreak of 2019-nCoV, understanding the nature and associated molecular mechanism of this virus accompanying its clinical characters is essential. 2019-nCoV possesses a positive sense single-strand RNA genome that is covered by an envelope. The genome consists of 29891 nucleotides and codes for 9860 amino acids. The genome structure is as follows: 5UTR-S-E-M-N-3UTR (S, E, M, and N). It consists of six ORFs. In cells expressing ACE2, 2019-nCoV applies ACE2 as a receptor for entry [43]. 2019-nCoV possesses a positive sense single-strand RNA genome that is covered by an envelope. Understanding the molecular details of 2019-nCOV in order to find new targets to treat effectively are pivotal [44]. PAMPs (ssRNA or dsRNA) are determined by RNA-receptor, TLR7 and 8 for ssRNA and for replicating virus by cytosolic RNA sensor, RIG/MDA5. This recognition step will result in the activation of several signaling pathways, which leads to TF production at last. Produced TFs include NF-KB, AP-1, IRF3, and IRF7. Their production leads to the expression of genes, which are responsible for encoding the molecules, required for an inflammatory response such as cytokines (for example TNF and IL-1) and also chemokines (for example CXCL8 and CCL2). The production of IRF3 and IRF7 leads to IFN-type I production, which is critical for an innate immune response against virus infection and replication. 2019-nCOV suppresses the response to viral infection through IFN type I. Humoral response (especially the neutralizing antibodies production) has a protective role due to the prevention of infection in later phases and prevention of re-infection. 2019-nCoV leads to the induction of IgG production against N protein which results in a reduction in serum level of memory B cells. 2019-nCoV induces lymphocyte apoptosis, which leads to lymphopenia. Thus, immunopathology can play a relevant role in disease development. Analysis of viral proteins finds 2019-nCoV has several changes, including loss of ORF3b and a short truncation of ORF6 that potentially affect its capacity to modulate the type I IFN response. Together, this augmented type I IFN sensitivity is likely for its successful pretreatment. Therefore, IFNβ1 can be considered safe and easy to upscale treatment against COVID-19 infection Taken together, 2019-nCoV is closely related to cytokine storm, resulting in diffuse damage of lung cells, pulmonary fibrosis, and multiple organ damage, even death. It can be treatment by anti-shock therapy, support and symptomatic treatment, Inhibition of excessive immune cell activation and cytokine production, hormone therapy, nonsteroidal anti-inflammatory drugs, and neutralizing monoclonal antibodies against elevated cytokines to prevent severe disease and death [45]. All of the above information can give scientists the chance to develop novel and specific molecules to target the virus life cycle to eradicate the infection completely. Regarding the short-term protection and prevention of viral infection, the implementation of COVID-19 emerging control is vital.

Conflict of Interest

All of authors declare that they have no conflicts of interest to this work.

Authors' Contributions

S.V conceived of the presented idea. S.V, M.M, M.S, and F.A. collected, interpreted and analyzed data and wrote the drafting of the article. Z.M, S.V, and M.M. developed, revised, and approved the theory. S.V. performed the critical revision and verified the whole concept. Z.M and S.V encouraged the other author to investigate and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Bibliography

1. Cyranoski D. "Mystery deepens over animal source of coronavirus". *Nature* 579.7797 (2020): 18-19.

2. Alberca GGF., *et al*. "Coronavirus disease-2019 and the intestinal tract: An overview". *World Journal of Gastroenterology* 27.13 (2021): 1255-1266.

3. Betaenou S., *et al*. "Atypical Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Children: A Review". *Current Pediatric Reviews* (2021).

4. Wang X., *et al*. "Challenges to the system of reserve medical supplies for public health emergencies: reflections on the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in China". *Bioscience in Trends* 14.1 (2020): 3-8.

5. Deng YY., *et al*. "Single-cell RNA sequencing data suggest a role for angiotensin-converting enzyme 2 in kidney impairment in patients infected with 2019-nCoV". *Chinese Medical Journal (Engl*) 133.9 (2020): 1129-1131.

6. Corman VM., *et al*. "Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR". *Euro Surveillance: Bulletin Europeen sur les maladies transmissibles = European Communicable Disease Bulletin* 25.3 (2020).

7. Ravikanth R. "Diagnostic accuracy and false-positive rate of chest CT as compared to RT-PCR in coronavirus disease 2019 (COVID-19) pneumonia: A prospective cohort of 612 cases from India and review of literature". *The Indian Journal of Radiology and Imaging* 31 (2021): S161-S169.

8. Li J-Y., *et al*. "The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future". *Microbes and Infection* (2020).

9. Cyranoski D. "Did pangolins spread the China coronavirus to people?" *Nature* (2020).

10. Bai WZ., *et al*. "Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2". *Journal of Medical Virology* (2020).

11. Benvenuto D., *et al*. "The 2019-new coronavirus epidemic: Evidence for virus evolution". *Journal of Medical Virology* 92.4 (2020): 455-459.

12. Angeletti S and Benvenuto D. "COVID-2019: The role of the nsp2 and nsp3 in its pathogenesis" (2020).

13. Zeiss CJ., *et al*. "Animal Models of COVID-19. I. Comparative Virology and Disease Pathogenesis". *ILAR Journal* 9 (2021).

14. Cheng J., *et al*. "The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients". *Journal of Medical Virology* (2020).

15. Cong Y., *et al*. "Nucleocapsid Protein Recruitment to Replication-Transcription Complexes Plays a Crucial Role in Coronaviral Life Cycle". *Journal of Virology* 94.4 (2020): e01925-02019.

16. Chan JF., *et al*. "Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan". *Emerging Microbes and Infections* 9.1 (2020): 221-236.

17. Chan JFW., *et al*. "Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan". *Emerging Microbes and Amp; Infections* 9.1 (2020): 221-236.

18. Shen Z., *et al*. "Genomic diversity of SARS-CoV-2 in Coronavirus Disease 2019 patients". *Influenza and Other Respiratory Viruses* (2020).

19. Qin C., *et al*. "Dysregulation of immune response in patients with COVID-19 in Wuhan, China". *Clinical Infectious Diseases* (2020).

20. Coutard B., *et al*. "The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade". *Antiviral Research* 176 (2020).

21. Paraskevis D., *et al*. "Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event". *Infection, Genetics and Evolution* (2020): 104212.

22. Wen F., *et al*. "Identification of the hyper-variable genomic hotspot for the novel coronavirus SARS-CoV-2". *The Journal of Infection* 80.6 (2020): 671-693.

23. Biswas N., *et al*. "Structural and Drug Screening Analysis of the Non-structural Proteins of Severe Acute Respiratory Syndrome Coronavirus 2 Virus Extracted From Indian Coronavirus Disease 2019 Patients". *Frontiers in Genetics* 12 (2021): 626642.

24. Chen Y., *et al*. "Structure analysis of the receptor binding of 2019-nCoV". *Biochemical and Biophysical Research Communications* 525.1 (2020): 135-140.

25. Seyran M., *et al*. "The structural basis of accelerated host cell entry by SARS-CoV-2dagger". *The FEBS Journal* (2020).

26. Phan LT., *et al*. "Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam". *New England Journal of Medicine* 382.9 (2020): 872-874.

27. Shanmugaraj B., *et al*. "Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19)". *Asian Pacific Journal of Allergy and Immunology* 38.1 (2020)10-18.

28. Market M., *et al*. "Flattening the COVID-19 Curve With Natural Killer Cell Based Immunotherapies". *Frontiers in Immunology* 11 (2020): 1512.

29. Morse JS., *et al*. "Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV". *ChemBioChem* 21.5 (2020): 730-738.

30. Liu Y., *et al*. "Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury". *Science China Life Sciences* 63.3 (2020): 364-374.

31. Zhang DH., *et al*. "In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus". *Journal of Integrative Medicine* 18.2 (2020): 152-158.

32. Habibzadeh P and Stoneman EK. "The Novel Coronavirus: A Bird's Eye View". *Journal of Medical Virology* 11.2 (2020): 65-71.

33. Richardson P., *et al*. "Baricitinib as potential treatment for 2019-nCoV acute respiratory disease". *The Lancet* 395.10223 (2020): e30-e31.

34. Stebbing J., *et al*. "COVID-19: combining antiviral and anti-inflammatory treatments". *Lancet Infectious Disease* 20.4 (2020): 400-402.

35. Russell B., *et al*. "Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence". *Ecancermedicalscience* 14 (2020): 1022.

36. Tetro JA. "Is COVID-19 receiving ADE from other coronaviruses?" *Microbes and Infection* 22.2 (2020): 72-73.

37. Chen L., *et al*. "Convalescent plasma as a potential therapy for COVID-19". *Lancet Infectious Disease* 20.4 (2020).

38. Name JJ., *et al*. "Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity". *Frontiers in Nutrition* 7 (2020): 606398.

39. Tabibi S., *et al*. "Therapeutic Plasma Exchange: A potential Management Strategy for Critically Ill COVID-19 Patients". *Journal of Intensive Care Medicine* 35.9 (2020): 827-835.

40. Tian X., *et al*. "Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody". *Emerging Microbes and Infections* 9.1 (2020): 382-385.

41. Persad G., *et al*. "Public Perspectives on COVID-19 Vaccine Prioritization". *JAMA Network Open* 4.4 (2021): e217943.

42. Society of Pediatrics CMA, Editorial Board CJoP. "Recommendations for the diagnosis, prevention and control of the 2019 novel coronavirus infection in children (first interim edition)". *Zhonghua Er Ke Za Zhi* 58 (2020): E004-E.

43. Han Q., *et al*. "Recent insights into 2019-nCoV: a brief but comprehensive review". *The Journal of Infection* 80.4 (2020).

44. Guzzi PH., *et al*. "Master Regulator Analysis of the SARS-CoV-2/Human Interactome". *Pathogens* 9.4 (2020).

45. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *The Lancet* 395.10223 (2020): 497-506.

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