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A review of the latest research and development of the pathogenesis and treatment of COVID-19

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Abstract. The novel coronavirus is a respiratory transmitted disease caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-Cov-2). The outbreak of the novel coronavirus disease 2019 (COVID-19) began in China at the end of 2019. It is surprisingly highly contagious, and the original virus has a strong fatality rate. Scientists responded quickly to study the structure and genomic characteristics of the virus, gained an in-depth understanding of the infection characteristics and pathogenesis of the virus, and provided valuable experience for the clinical diagnosis and treatment of the novel coronavirus. At present, scientists are actively working on vaccines and treatments to meet the challenges of the novel coronavirus. Although some breakthroughs have been made in vaccine research and development, the global epidemic is still serious. This article summarizes the latest research results in order to provide inspiration for the control, diagnosis, treatment, and prevention of COVID-19 so as to protect people's life and health.

Keywords: COVID-19, SARS-CoV-2, spike protein, T cells.

1. Introduction

Novel Coronavirus Pneumonia brought on by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, China in December 2019. The SARS-CoV-2 infection-related illness was formally referred to as Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020. Fever, dry cough, and exhaustion are among the main clinical symptoms of COVID-19, while some pulmonary symptoms are also included. A majority of the general population is susceptible to infection since SARS-CoV-2 is highly contagious. At present, sick individuals and wild animal hosts are the main origins of the illness, which is spread through respiratory droplets and direct contact. Following the virus's spread, the scientific community and Chinese government responded swiftly to recognize the pathogen, share the genetic sequence of the virus, and implement prevention strategies. In this paper, the author reviews the current studies that have uncovered the key aspects of biology and disease pathogenesis of SARS-CoV-2 [1], as well as its clinical characteristics, diagnosis, and treatment, which includes the related drug and vaccine development. This review tries to provide consensus among experts by summarizing the latest research results. Ongoing initiatives and experiences from China are also discussed, which could help with outbreak containment, thus expanding people’s knowledge of this newly emerging infectious illness, and providing updated advice on how to avoid, manage, and—most importantly—control the epidemic.

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2. The structure of a coronavirus

There are four main subpopulations of coronaviruses: α, β, γ, and δ. Six viruses make up the alpha coronavirus family, including the human diseases CoV229E and CoVHKU1. CoVOC43, SARS-CoV, and MERS-CoV are examples of human diseases that belong to the beta coronavirus category [2]. The amino acid sequences of 7 conserved domains in the genome's Open Reading Frame 1AB share 94.6% homology with the original SARS-CoV, and SARS-CoV-2 is also a β-coronavirus [3]. Coronavirus particles are usually round or polymorphic. They have a diameter of 120–160 nm and are made up of Spike (S) proteins, a signature of coronaviruses. During infection, the S protein mediates viral attachment and membrane fusion [4]. The coronavirus genome normally encodes three more structural proteins. Apart from distinctive S proteins, there are also Membrane (M) proteins, Envelope (E) proteins, and Nucleocapsid (N) proteins. The number of amino acids (aa) in M proteins is between 218 and 263, the number of aa in E proteins is between 74 and 109, and the number of aa in N proteins is between 349 and 470. Generally, there are 20 copies of E protein in each virion, and N protein is a phosphorylated RNA-binding protein that helps genomic RNA properly fold into the nuclear capsid.

3. Genomic characterization of SARS-CoV-2

The forward single-stranded 29891 bp RNA genome of the SARS-CoV-2 virion has a diameter of 60 to 140 nm. The genome sequence alignment revealed that SARS-CoV-2 and RaTG12, a virus isolated from bats in Yunnan, China, shared 93.1% sequence identity [5]. These findings imply that a virus specific to this kind of bat may have given rise to SARS-CoV-2. Insertional comparative genomic analyses imply that pangolins are the most plausible intermediate hosts for cross-species transmission, based mostly on sequences obtained from coronavirus S proteins isolated from these mammals. Two novel insertions and roughly 30 ORFs were discovered when the SARS-CoV-2 and SARS-CoV genomes were analyzed together. The ORF6, ORF8, and S genes of the SARS-CoV and BAT-CoV genomes displayed minimal sequence conservation across coronaviruses. However, BAT-SL-CoVZC45, BAT-SL-CoVZXC21, and RaTG13 viruses are in general very similar to SARS-CoV-2, especially ORF8 [6], of whom there are several variants encoded by the SARS-CoV-2 genome [7]. These findings may contribute to a deeper comprehension of ORF8's role in SARS-CoV-2.

4. Infectious properties of S proteins from SARS-CoV-2

The S protein of SARS-CoV-2, similar to that of SARS-CoV, interacts with angiotensin-converting enzyme 2 (ACE2) and initiates the entry of the virus into human lung type II cells [7]. There are 2 main domains for the S protein, namely the N-terminal S1 domain which mediates the binding to ACE2, and the C-terminal S2 domain which facilitates the fusion of the viral membrane with the host cell membrane [8]. The S1 subdomain 424–494 aa is known as the receptor binding domain. The peptidase domain, the extracellular binding site on ACE2, is directly in contact with this motif [9]. Arginine R667 and R797 are the two cleavage sites for the S protein. S1 and S2 are connected by the R667 site, and when R797 is cleaved, the final S2 turns into a polypeptide [10]. Several cellular proteases, such as cathepsin L, trypsin, and elastase, can cleave the S sequence at these two locations. For the entrance of SARS-CoV and SARS-CoV-2 to the host cells, the two S protein sites must first be cleaved. For the binding of S1 to ACE2, the first S protein site is crucial, and the second S protein site is necessary for membrane fusion.

5. Pathology and disease pathogenesis

The pulmonary status of a 50-year-old male patient was described in great detail in the postmortem report. Acute respiratory distress syndrome (ARDS), which results in alveolar cell loss, hyaline membrane development, interstitial inflammation, and significant lymphocytic infiltration, caused this patient's death. In the interalveolar area, virus-like cytopathic alterations such as multinucleated syncytial cells and abnormally expanded alveolar cells were also found [11]. It is possible that COVID-19's pathophysiology resembled SARS to some extent. Human airway epithelial cells and alveolar cells are both cytopathic and affected by viral infection. Immune-mediated damage, like the reaction to the SARS coronavirus, may be important in the pathogenesis of COVID-19, particularly in those who are

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very unwell. The production of cytokines, such as transforming growth factor-β1, tumor necrosis factor-α, interleukin-1β, interleukin-6, and other chemokines for circulating leukocytes, is promoted by viral infection of alveolar cells. In severe COVID-19, a variety of subsequent inflammatory chain reactions may lead to cytokine storm. Current research has found that the levels of cytokines in serum were increased, including interleukin-2, interleukin-7, interleukin-10, granulocyte colony-stimulating factor, monocyte chemoattractant protein, and tumor necrosis factor-α [12]. Cytokine storm is considered a critical factor leading to ARDS and extrapulmonary organ failure. Peripheral lymphopenia is a common phenomenon, especially associated with severe COVID-19. This discovery may be functional compartmentalization because these cells seem to be drawn to virus-infected lung tissue rather than any particular virus-mediated suppression. The proportion of activated HLA-DR+CD38+T cells in the peripheral blood was noticeably higher despite the decrease in total numbers. Likewise, compared to the number of CD8+T cells, there was a growth in the number of CCR4+CCR6+Th17 cells and the subgroup of CD4+T cells with cytotoxic properties [13]. These preliminary findings thus point to an essential role for T cells in modifying the COVID-19-associated pneumonia response, while mechanistic investigations using suitable animal models and human lung materials are still required to fully assess this matter.

6. Introduction of anti-COVID-19 drugs

Currently, drugs for COVID-19 mainly include antiviral drugs and anti-inflammatory drugs. Antiviral drugs, such as remdesivir, can interfere with the replication process of viral RNA. Remdesivir shows good antiviral activity in vitro and animal experiments and has shown certain efficacy in some clinical trials [13]. Ritonavir, which can block viral replication, was previously used in the treatment of Acquired Immune Deficiency Syndrome (AIDS), but some studies have shown that ritonavir can also be used to treat COVID-19 [13]. Anti-inflammatory drugs such as Norepinephrine (NA) can inhibit the inflammatory response and thus reduce mortality. A study conducted in China found that the mortality of the NA treatment group was significantly reduced [14]. In conclusion, these drugs have all achieved preliminary efficacy. However, further experiments are needed to determine their safety and efficacy.

7. Introduction of mainstream COVID-19 vaccines

The following COVID-19 vaccinations are presently widely used:

Pfizer-BioNTech vaccine (BNT162b2): A Pfizer and BioNTech-created mRNA vaccine was given emergency use authorization (EUA) by the American Food and Drug Administration (FDA) in December 2020. This vaccine utilizes mRNA technology to enable human cells to produce a portion of the SARS-CoV-2 virus, thereby triggering an immune response. Clinical trials have shown an efficacy rate of over 95% for this vaccine [15].

Moderna vaccine (mRNA-1273): This mRNA vaccine was developed by Moderna and gained authorization for emergency use from the European Medicines Agency in December 2020. Similarly, it employs mRNA technology to stimulate human cells to produce the SARS-CoV-2 virus protein and induce an immune response. Clinical trial findings have demonstrated an efficacy rate of 94.1% for this vaccine [16].

AstraZeneca vaccine (AZD1222): This vaccine was created by AstraZeneca, in cooperation with the University of Oxford. It uses an adenovirus vector. It involves inserting the genetic material of the SARS-CoV-2 virus protein into a harmless adenovirus, and then injecting it into humans to trigger an immunoreaction. Clinical trial results showed an average efficacy of 70.4% under different doses and injection regimens [17].

Sputnik V vaccine: This vaccine was created by researchers at the National Research Center for Epidemiology and Microbiology in Russia. It was approved by the Russian Ministry of Health. It is a vector vaccine consisting of two different adenoviruses (Ad5 and Ad26). Clinical trial data has revealed an efficacy rate exceeding 90% for this vaccine [18].

Johnson & Johnson vaccine (Janssen COVID-19 Vaccine): Developed by Janssen Pharmaceuticals, this vaccine is a viral vector vaccine that uses a modified adenovirus to deliver the genetic instructions

for producing the SARS-CoV-2 S protein. It received EUA from the FDA in February 2021. Clinical trials have shown an overall efficacy rate of 66.3% in preventing moderate to severe COVID-19. Besides, it has demonstrated 85% effectiveness in preventing severe disease and hospitalization [19].

Sinovac vaccine (CoronaVac): This is an inactivated vaccine developed by Sinovac, a Chinese biopharmaceutical company. The SARS-CoV-2 virus is used in an inactivated form to elicit an immunological response. Several countries, particularly in Latin America, have authorized its emergency use. Clinical trials have shown varied efficacy rates ranging from 50.65% in Brazil to 91.25% in Turkey [20].

The above-mentioned vaccines are currently widely used worldwide. They have undergone large-scale clinical trials in multiple countries and obtained approvals and authorizations from relevant agencies. Continued monitoring and research are essential in order to assess their long-term safety and efficacy. Vaccination efforts and strategies may vary from country to country based on availability, regulatory approvals, and public health guidelines.

8. Conclusion

Since the COVID-19 outbreak, the Chinese people have aggressively responded to and battled against the disease with the help of the Chinese government. With the continuous efforts of scientists, people now can have a clear understanding of the structure and genetic composition of SARS-CoV-2. In addition, some targeted drugs and vaccines have been found through the infection characteristics of their special structure and pathogenesis. However, many pressing issues remain, for example, whether SARS-CoV-2 is likely to mutate to produce new strains and whether new coronaviruses will coexist with humans for a long time. The main host source of SARS-CoV-2 is currently unknown, and no specific medication has been created to completely cure SARS-CoV-2. To provide the development of vaccines and drugs a clearer direction, more research is required and every discovery is crucial to overcoming COVID-19.

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