REVIEW ARTICLE

An Insight into the Pragmatic Pandemic: How Remote are we Still in Breaching the Scientific Barriers of Severe acute respiratory syndrome virus-2?

Nirupa Elisetti

ABSTRACT

Coronavirus disease-19 caused by severe acute respiratory syndrome virus-2 is the global health emergency which has been ruining the normal livelihood of people across the world. Researchers are still striving hard to discover solutions that would help in containment of this contagion. This lethal virus though not messing up the mortality rates with the infected proportions, yet the significant counts of deaths remain alarming. Incessant learning of the diverse characteristics of the virus has been still in process by scientists across the nations. This particular review discusses about coronavirus and its specific spike protein mediated entry into the host disturbing the human immunological equilibrium with apparent symptomology. This is a systematic summarized review of various aspects of the virus, taxonomy of the disease, host immune reactions, and its therapeutic approaches.

KEY WORDS: Coronavirus, Coronavirus disease -19, severe acute respiratory syndrome virus-2, spike protein.

Introduction

Viruses are miniature contagious agents much smaller than the bacteria and not detectable under a normal microscope. They are minuscule obligate intracellular infectious structures that need a host (humans or any other organism) for their survival and replication. They are infectious to any living organisms from humans, animals, plants to microorganisms that include bacteria, etc. The highly contagious part of a virus particle is called "virion" which is unique to individual viruses among many of them classified as seen under an electronic microscope. The viruses are further classified based on their morphological structure, chemical composition (either DNA or RNA), and mode of replication.[1]

Coronaviruses are a large group of positive polarity single-stranded RNA (ribonucleic acid) genome which ranges from 26 to 32 kilobases in length that comes under the order of "Nidovirales." Coronaviruses are named so because of their crown-like morphology as seen in an electron microscope in 1968.[2] These coronaviruses are further segregated into alpha, beta, gamma, and delta coronaviruses. Coronaviruses have been recognized to have avians as hosts but also identified in various other animals such as cats, camels, masked palm civets, bats, mice, and dogs. Mammalian coronaviruses are very rare to occur, but unfortunately, their incidence has been still identified, increased, and severe.[3] The two notable well-known mammalian pathogenic coronaviruses identified so far are severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle-East respiratory syndrome (MERS-CoV) apart from the present pandemic.[3] SARS-CoV first originated with an index case in the Guangdong province of South China in 2002 and the virus was isolated in 2003. It was thought to be from bats yet uncertain which later spread to civet cats before infecting humans. This global outbreak affected 26 countries with more than 8000 cases in 2003.[4] MERS by MERS-CoV was first indexed in Jordan (Saudi Arabia) in April 2012 with 2494 confirmed cases and 858 fatalities. The largest later outbreak again was identified in 2015 in the Republic of

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Chief Dental Surgeon, Department of Periodontics and Implantology, Nirupa's DENTAL ZONE, Hyderabad, Telangana, India

Address for correspondence:

Dr. Nirupa Elisetti, Nirupa's DENTAL ZONE, Nallagandla, Hyderabad, Telangana-500019, India. Phone: +91-6309072369.
E-mail: nirupasdentalzone@gmail.com

Korea from a traveler returning from the Arabian Peninsula.[5]

Taxonomy

The present virus which is shivering mankind and devastating their livelihood is the novel coronavirus-2019. The World Health Organization (WHO) recommends a new name to the virus as a novel coronavirus (2019-nCoV) where "n" stands for novel and "CoV" stands for coronavirus.[6] International Committee on Taxonomy of Viruses has named it as "Severe acute respiratory syndrome virus 2" (SARS-CoV-2) based on its species group it belongs to SARS-related coronavirus.[7,8] However, the WHO in its situation report released on February 11, 2020, has named the disease as coronavirus disease (COVID)-2019, in short for "Coronavirus disease 2019," wherein, as the disease is identified in the year 2019 it is named so as "-19."[9]

Background

A nightmare in late December 2019, an index case of respiratory pneumonia as reported in Wuhan Hubei province of China. In the next few days, a cluster of cases with similar clinical characteristics raised doubt of disease resemblance and also from the same location of the Huanan seafood market in Wuhan where non-aquatic animals are sold. Environmental sampling of the same also confirmed a similar virus with that of the people suffering from respiratory pneumonia. This group of viruses showed resemblance with the SARS group of viruses and so named as SARS-CoV-2 and later renamed by the WHO as COVID-19.[9]

Pathogenesis

Transmission

The recent outburst of mammalian coronavirus SARS-CoV-2 was identified to cause pneumonia by infecting the lower respiratory tract. The severity seems to be on a lower side as compared to SARS-CoV1 and MERS (pathogenic coronavirus identified to date apart from recent pandemic). It falls under beta coronaviruses which are pathogenic to humans and it is thought to have originated from an avian host before invading man. Based on genomic sequence matching analysis, it was identified to have a close association with bat SARS-like beta coronaviruses, since there was 90% similarity in sequence proteins. Furthermore, the spike structural protein similarity was also matched with 93% sequence identity with bat coronaviruses.[10] Nevertheless, of bats being the origin in this scenario with shreds of evidence, there are thoughts of an intermediate host before the virus jumping from bats to man. This introspection arises due to the fact of the role of an intermediate host in both SARS-CoV and MERS-CoV, wherein bats acted as natural reservoirs and masked palm civet for SARS-CoV and dromedary camels for MERS-CoV were intervening between before terminating into the man. The Huanan seafood market where the index cases of COVID-19 have been linked does not sell non-aquatic animals which further ignited the researchers to focus on the role play of an intermediate host. Human-to-human transmission has been confirmed as there were cases reported with no travel associated with the seafood market and were among the close family members.[11,12] This transmission is thought to occur through droplets by coughing or sneezing from the infected person. Fomites (objects or materials in which an infected person comes into contact with the infective agents on it) are also convicted to spread the disease.[13] Vertical transmission from a mother to child is still under research with no confirmed evidence of spread. However, pregnant mothers are susceptible to this virus as the geriatric population relative to other population groups. A study conducted in nine third trimester mothers in Wuhan city had shown that none of the nine neonates born by C-section were infected with SARS-CoV-2.[14]

Genomic characteristics of coronavirus and its entry into cells

Coronavirus has a positive sense RNA of 29.9 kb and also has numerous open reading frames (ORF) (6-11). These ORFs help in the production of various non-structural proteins (NSPs) along with accessory and structural proteins. However, the main structural proteins identified are spike(S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein. The various accessory proteins produced interfere with the host immune response.[15] A virion (virus particle) enters into the host cell for it to explode and disturb host well-being before manifesting the various disease characteristics as clinical symptoms. Viral entry plays a crucial role which is the initial step in disorganizing the prosperity of the host. This occurs through the interaction of the virus with the host cell by their structural proteins. The intrepidity of coronavirus begins with its binding with a specific host receptor followed by host cell membrane fusion and then delivers its nuclear material into the target cell. The linchpin here is the spike structural protein

which accords a decisive role for the ingress of the virus particle into the host cell. It assembles itself as a trimer on the surface of the virus presenting as two domains S1 and S2. S1 is the N-terminal domain for it to bind to cell surface receptor and S2, a C-terminal domain accountable for fusion.[16]

The characteristic "corona" or "crown shape" of the virus is for its trimeric congregation on virion surface. On discovering a susceptible receptor (like ACE-2 in humans), the S1 domain of spike protein which possesses a "Receptor binding domain" is released due to certain conformational changes of the spike protein. Once binding to the S1 domain is completed the fusion of the host cell surface to the membrane-anchored S2 domain results in a syncytial formation and now the virion injects its nuclear RNA into the host cell.[17] Research has been continuously focusing on the virus attachment to the host cell in particular. This is because for SARS-CoV-2 entry to host cell S-protein has to be cleaved to separate itself as S1 and S2 by cellular proteases. S1 assists in binding to receptor and S2 for cellular fusion with host cell membranes and further releases proteases to dissolve the host cell membrane and gain entry into the host cell. The whole process of spike protein splitting itself into S1 and S2 domain is called S protein priming mediated by transmembrane protease serine 2 (TMPRSS2).[18,19] TMPRSS2 also assists in viral replication through unknown mechanisms. The remaining proteins M and E proteins are committed for the new viral envelope formation and N protein is associated with the formation of helical ribonucleocapsid complex with positive-sense single-stranded RNA.[20] M protein is another transmembrane protein for transport of nutrients and the release of new virion buds. N protein along with E protein and almost 16 nonstructural proteins (nsp1-nsp16) interfere and provoke the host immune response.[15]

Target receptors

Angiotensin-converting enzyme-2 (ACE2) is the target receptor of SARS-CoV-2 like SARS-Co viruses. ACE2 gene is expressed on X-chromosome. It is a zinc carboxypeptidase ectoenzyme with one catalytic site and its N-terminus present toward extracellular space. ACE2 is dispersed throughout our body and is more concentrated on the lungs. They are also found on hearts, kidneys, gastrointestinal tract, etc.[21] The distribution of ACE2 includes bronchial, pulmonary epithelium, and pulmonary capillaries. ACE2 exhibits a protective function on the heart and lungs by way of conversion of angiotensin-ii to angiotensin (1-7) and MasR (Mas receptor), thus blocking the deleterious effects caused by angiotensin II which includes angiogenesis, vasoconstriction, and inflammation.[22,23]

Lung ACE2 receptor is the key to the entry of coronavirus into the human body. The spike protein attachment to the catalytic site of ACE2 with the help of its S2 domain and serine protease (TMPRSS2) is very much essential for its ingress. This is followed by a conformational change in spike protein by proteases and a cleavage results in the S2 domain which facilitates fusion of envelope with the host cell membrane. This terminates in successful access of coronavirus (SARS-CoV-2) nuclear material into the host cell and the beginning of COVID.[24] Thus, hypothetically if the ACE2 expression is less in the body, then the prevalence of infection should also decrease due to fewer sites for SARS-CoV-2 to approach. In contrast, since ACE2 protects the lungs, decreased ACE2 expression is deleterious to the lungs.[21] Increased male expression of ACE2 is observed and so disease severity is more in males compared to females which are under research. On a similar note, due to decreased maturation of ACE2 in children, it is observed that the symptoms and disease severity are mild. As age increases, maturation of ACE2 also occurs.[25]

Role of body defense against corona virus

As with any external stimuli, the first defense mechanism of the human body is innate immunity which includes many immune and non-immune cells. They react as a first-line defense against infection but not as long-lasting protective immunity. Adaptive or acquired immunity produces a group of specific immune cells against specific infections and thus plays a very important role in immunological memory.[26] This acts as a protective mechanism on reexposure of the infective agent which is the basis for vaccine-based immunity. Similarly, when coronavirus gains entry into susceptible cells with its spike protein through ACE-2 receptors present predominantly on the respiratory epithelium, numerous inflammatory cells are recruited through molecular patterns. Pro-inflammatory cytokines and chemokines which include CL8, CXCL10, C3a, and C5a are released which, in turn, stimulate various other inflammatory cells such as monocytes/macrophages, granulocytes, and natural killer cells that release interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, and interferon-γ causing damage in the lower respiratory tract.[27]

The observed mortality rate due to COVID-19 is contributed mainly to a hyperinflammatory reaction against SARS-CoV-2 which is specifically "Cytokine storm" or "Macrophage activated syndrome." Cron and Behrens defined "Cytokine storm" as an auto-amplifying cascade of cytokine production due to increased host immune response.[28] This results when white blood cells/leukocytes are activated leading to an upsurge in cytokines predominantly TNF-α, IL-6, IL-β, and IL-10 which are life threatening due to multiorgan failure. COVID-19 has a specific increase in the IL-6 cytokine level. Cytokine storm is thought to suppress both the host innate and adaptive immune response against SARS-CoV-2. TNF-α and IL-β levels are also raised along with IL-6 as observed in COVID-19 patients.[29] The acute-phase proteins increased include C-reactive protein (CRP), serum amyloid A, and ferritin signifying role of the innate immune response. It has also been observed that there is depletion of T-cell subsets and exhaustion of CD8 T cells from adaptive immune cells. TNF-α-mediated evacuation/apoptosis of T-cells with suboptimal responses has been noted.[30] Hyperactivation of CD8 + T cells enhances perforin and granulysin with increased lung injury. As a result vascular leakage and intravascular coagulation occurs due to the death of endothelial cells by cytokine storm leading to damage of blood vessels in the lungs. This upsurge of inflammatory cytokines/cytokine storm could result in apoptosis of both epithelial and endothelial cells of the lung which is manifested as diffuse alveolar damage, pleural effusion, edema, and lung consolidation along with focal hemorrhages. Severe lung damage and multiorgan failure are the main cause of death in COVID-19 patients.[31,32]

Symptomology and immunological findings

The most frequent symptoms identified in patients were dry cough, sore throat, myalgia, fatigue, pyrexia, anorexia, and dyspnea. Pathological findings observed were decreased lymphocyte count, increased CRP, and ferritin.[33] There are depleting counts of CD4+ lymphocytes in severely ill patients. IL-6 and TNF-α are also seen to rise in patients admitted to the intensive care unit with decreased oxygen saturation <93% with resting respiratory rate >30 breaths/min. Computerized tomography findings reveal ground-glass opacity along with the consolidation of lungs. Diffuse lesions as observed in severely ill patients.[34]

Xiong *et al*. have observed that SARS-CoV-2 activates P53 (responsible for cell survival) signaling leading to apoptosis of lymphocytes, thus leading to lymphopenia.[29] Chen *et al*.[35] demonstrated lymphoid tissue damage, splenic nodular atrophy, and lymph follicle depletion. This could be a result of infected CD169+ macrophages in spleen and lymph nodes by SARS-CoV-2. Fas/FasL interactions cause activation-induced cell death by CD169+ macrophages. Lymphopenia occurs also due to the stimulation of macrophages by SARS-CoV-2 to induce IL-6, TNF-α, and IL-1β which directly promote lymphocytes necrosis. Thus, increased IL-6 plays a crucial role along with neutrophil chemotaxis and lymphocyte depletion/necrosis in the pathology of COVID-19.[30]

Suggested potential treatment modalities

No definitive treatments have so far been identified. Prospective treatment options include symptomatic relief of COVID-19 affected patients. Adequate isolation of the patient is an essential aspect to prevent further spread and also adds to confinement of disease.[36,37] Treatment is focused on symptoms associated which include cough and fever medication. Antiviral medication such as "Remdesivir" has shown good results to a certain extent in some cases. Remdesivir also was promising against many viruses.[38] Xaio *et al*. have observed the effectiveness of remdesivir against COVID-19 *in vitro*. However, it still needs to be authenticated for its uncertainty. Concurrently, chloroquine an antimalarial drug with immune modulatory function also has proven effective against SARS-CoV-2 *in vitro*.[39] Nevertheless, this again has to be demonstrated constructive in humans with a significant number of clinical trials.

Immunomodulators for cytokine storm

Immunosuppressants are thought to be administered in severely ill hospitalized patients to downregulate the amplifying immune cells responsible for severe damage to lungs and multiorgans. IL-6 inhibitors like tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody, prevent its binding to its receptor.[40] Cytokines are released in COVID-19 patients primarily to eliminate the viral load. Hence, the administration of immunosuppressants at an early stage of the disease is still controversial. IL-6 is observed to increase exponentially in intensive care patients under oxygen therapy and severe lung damage. IL-6 inhibitors are under consideration for critical patients but research should still confirm its prognosis.[41] Corticosteroids (glucocorticoid therapy) administration in critically ill patients with

coronavirus infection is followed. At therapeutic doses, they help in immunosuppressive actions such as IL-1 and IL-6 downregulation, activation of T-cells, and macrophages.[42] They also inhibit cytokine proliferation and action predominantly pro-inflammatory cytokines such as IL-1, IL-6, IL-2, and TNF-α. Henceforth, the administration of glucocorticoids with appropriate dose, duration, and timing is crucial with its two-edge sword action in COVID patients.

Convalescent plasma therapy

One another prospective treatment modality that is followed includes the administration of plasma obtained from patients who have recovered from COVID-19. SARS-CoV-2-specific antibodies produced from recovered individuals and their serum helps in prevention of reinfection.[43] Therefore, plasma obtained from patients recovered from COVID-19 is used to extract immune globulins specific to SARS-CoV-2 and then administered to severely ill hospitalized patients.[44] Nonetheless, the safety of plasma therapy has to be further investigated. The binding of S-protein of SARS-CoV-2 to the catalytic site of the ACE2 receptor is more coherent, and regrettably, the antibodies of SARS-CoV are not recognizing the receptor-binding domain of SARS-CoV-2. Fortunately, sera of convalescent SARS patients are cross-neutralizing the spike protein-mediated entry of SARS-CoV-2 into the target cell.[18]

Conclusion

This potential novel coronavirus has handicapped the economic and public health infrastructure globally curbing a normal lifestyle. Prevention is always better than cure. Precautions should be strictly followed for containment of the SARS-CoV-2 virus and also from future viral outbreaks. Efforts should be made for the development of comprehensive preventive modalities to curb incidences of such potentially harmful viruses/diseases.

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Authors' Contributions

Dr. Nirupa Elisetti had the idea of the article and performed the literature search and data analyses. She has drafted and critically revised the work.

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