Mini Review
Open Access

Solving puzzle of the immunopathogenesis for management of COVID-19 disease

Abstract

A novel coronavirus (2019-nCoV) infection was first declared in December 2019 in Wuhan, Hubei Province, China. Coronavirus disease 2019 (COVID-19) is a variation of viral pneumonia, which is happened by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Today, the exact pathogenic mechanism of this viral infection in human remains unclear. COVID-19 is clinically very variable from being asymptomatic, mild to lethal manifestations such as multi-organ failure. There are not currently any specific therapy and/or vaccine for COVID-19 disease management. In this review, we aim to further explore puzzle of the immunopathogenesis in SARS-CoV-2 infection for improving of COVID-19 management.

Keywords: SARS-CoV-2, 2019-nCoV, COVID-19, pathogenesis, management

Volume 7 Issue 1 - 2020

Öner Özdemir,[1] Olena Erkun[2]
[1]Professor of Pediatrics, Division of Allergy and Immunology, Department of Pediatrics, Research and Training Hospital of Sakarya University, Turkey
[2]Resident in Pediatrics, Department of Pediatrics, Research and Training Hospital of Sakarya University, Turkey

Correspondence: Öner Özdemir, MD, Division of Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Sakarya University, Research and Training Hospital of Sakarya University, Adnan Menderes Cad., Sağlık Sok., No: 195, Adapazarı, Sakarya, Turkey, Tel + 90–(264) -444 54 00, Fax +90–(264) -275 91 92; Email ozdemir_oner@hotmail.com
Öner Özdemir - 0000-0002-5338-9561
Olena Erkun - 0000-0003-3067-3794

Received: May 06, 2020 | **Published:** May 25, 2020

Introduction

A novel coronavirus (2019-nCoV) infection was first declared in the end of December 2019 in Wuhan, China. Currently, the exact pathogenic mechanism of this viral infection in human remains unclear. In this review, our aim is to begin with virology, epidemiology and then continue with exploring pathogenesis/immunopathogenesis of SARS-CoV-2 infection and lastly finish with management.

Virology

There are some coronaviruses (CoV) known, namely OC43, 229E, HKU1 and NL63, which cause minor cold symptoms in human. And there are also three different types of coronaviruses known that can replicate in lower respiratory tract, and therefore, give rise to severe pneumonia and acute respiratory distress syndrome (ARDS).[1] These are severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and SARS-CoV-2.

The Coronaviridae family is a group of enveloped, positive-sense single-stranded RNA viruses with a wide variety of natural roots. These CoVs can manifest themselves as respiratory, entero-hepatic and neurologic diseases. The CoVs are genotypically and serologically categorized into 4 subfamilies: alpha-, beta-, gamma- and delta-CoVs. SARS-CoV and MERS-CoV are members of beta-CoVs. The virus element has a length of 60-100 nm and seems to be round or oval. The genomic sequence of SARS-CoV-2 is demonstrated to be mostly similar, nevertheless fairly diverse genomic composition compared to SARS-CoV and MERS-CoV.[2,3]

Epidemiology

The major route of transmission of SARS-CoV-2 is by means of breathing of airway droplets and contamination thru close contact. The highly infectious feature of SARS-CoV-2 is perhaps owing to the transmission by asymptomatic individuals. COVID-19 has a probable asymptomatic incubation period between 2 and 14 days, during which the virus might be spread. The most common predisposing elements of COVID-19 fatality are being elderly and having underlying diseases. The most prevalent manifestations of COVID-19 are fever, fatigue, myalgia and airway manifestations, together with cough, sore throat and dyspnea. Less frequent manifestations are phlegm production, headache, hemoptysis, and diarrhea. In most infected individuals, whose lungs are the host for a local infection, the immune response is enough for the recovery. However, in some people with dysfunctional immune response, viral antigens together with the sustained release of pro-inflammatory mediators from the environment of infected cells cause an uninhibited immune response that generates the enormous increase of immune cells and overproduction of cytokines. These patients also develop bilateral pneumonia and abundant mucus secretion in both lungs. Typically, findings of computer tomography (CT) images of the chest are bilateral multiple lobular and subsegmental areas of consolidation with characteristic pulmonary ground-glass opacity changes.[3,4] Blood tests show normal or decreased white blood cell count and lymphopenia.[5,6]

Ethio-pathogenesis

SARS-CoV-2 is a cytopathic virus. It induces injury and cause death of the cells and tissues, and it infects as part of its usual replicative process. Coronaviruses are enveloped viruses with corona-like protrusions, or spikes. These spikes are blamed for attacking and infecting host cells. Once the cell is infected, the viral ribonucleic acid, a single-stranded RNA, reproduce in the cytoplasm of the affected cell using viral RNA-dependent-RNA polymerase. The resulting offspring virions escape from the infected cell by budding, while they obtain their new envelopes from the cell membrane. Hence, SARS-CoV-2 infects and hijacks host cells, but distinct from non enveloped viruses, does not lyse cells. Infection of the airway epithelial cells and following replication of the virus in these tissues possibly gives

rise to increased levels of virus-mediated apoptosis with linked vascular leakage. Therefore, SARS-CoV-2 does not result in a straight destructive outcome of the infected cells.[3,5]

The primary infection location of SARS-CoV-2 is unclear and the pathogenesis of COVID-19 is still under investigation. For the majority of patients, COVID-19 may involve only pulmonary tissue, since it is principally an airway disease. Primary viral replication occurs in the mucosal epithelium of upper airway and in the gastrointestinal mucosa, causing a mild viremia. Most of the infections are restricted and become asymptomatic. In vitro experiments show that SARS-CoV-2 uses angiotensin convertase enzyme 2 (ACE2) receptors of the host cells for cellular entry. This might be significant for disease development since the failure of lung ACE2 receptor function is related with acute lung injury. ACE2 receptors are also expressed in several organs, including lungs, heart, kidneys and intestines, and on endothelial cells. Whether vascular derangement in COVID-19 is thanks to endothelial cell participation is now unidentified. Interestingly, SARS-CoV-2 can straightly infect engineered human blood vessel organoids in vitro. In a standard adult human pulmonary tissue, ACE2 receptors are expressed chiefly in alveolar epithelial type II cells, which can play a role as a viral reservoir. These cells generate surfactant which decreases surface pressure, thus averting alveoli from collapsing, and consequently is significant for the gas exchange function of the pulmonary tissue. Damage to these cells could clarify the severe pulmonary failure seen in COVID-19 patients. The ACE2 receptor distribution in the body may elucidate the multi-organ dysfunction demonstrated in the infected patients.[3,6-8]

Immuno-pathogenesis

To raise an antiviral reaction, innate immunity has to identify the virus incursion regularly by pathogen-associated molecular patterns (PAMPs). For RNA viruses eg. coronavirus, it is identified that PAMPs in the structure of viral genomic RNA, or the intermediaries throughout viral replication comprising dsRNA, are acknowledged either by endosomal RNA receptors, TLR3 (toll-like receptor 3) and TLR7, or by cytosolic RNA sensor, RIG-I/MDA (retinoic acid-inducible gene I/melanoma-differentiation-associated gene).[3,9] This identification event leads to start of the downstream signaling cascade, i.e. NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and IRF3 (interferon regulatory factor 3), associated by their nuclear translocation. In the nuclei, these transcription factors stimulate expression of type I IFN (interferon) and other pro-inflammatory cytokines, and these preliminary responses include the first line guard against viral infection at the access site. Type I interferon (IFN) via IFNAR (IFN-alpha/beta receptor), in line, induces the JAK-STAT pathway, where JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2. STAT1/2 builds a complex with IRF9,[10] and jointly they travel into the nucleus to begin the transcription of IFN-stimulated genes (ISGs) under the control of IFN-stimulated response element (ISRE) including promoters.[11] A helpful rising of this type I IFN reaction should be able to inhibit viral replication and dissemination at the beginning of early stage. In an experimental mouse model of SARS-CoV infection, dysregulated type I IFN and inflammatory monocyte-macrophages are the key factors of fatal pneumonia.[4,11] As a result, exaggerated type I IFN release and the infiltrated myeloid cells are the chief reason of pulmonary dysfunction and negatively affect the result of the infection.

Usually, the Th1-type immune response takes place a dominant role in an acquired immunity to viral infections. Cytokine microenvironment caused by antigen presenting cells dictates the course of T cell responses. Helper T cells arrange the general acquired response, whereas cytotoxic T cells are essential in death of virus infected cells. Humoral immune response, particularly manufacturing of neutralizing antibodies, takes place a protective role by restraining infection at subsequent phase and thwarts reinfection in the future. In SARS-CoV infection, both T and B cell epitopes were widely charted for the structural S, N, M and E proteins.[3]

The majority of the cases having severe COVID-19 disease demonstrate significantly increased serum levels of pro-inflammatory cytokines involving IL-1β, IL-6, IL-2, IL-17, IL-8, G-CSF, IP10, MCP1, MIP1a (CCL33) and TNF, defined as cytokine storm.[1,2,3,5] In addition, C-reactive protein and D-dimer are detected to be extraordinarily high. Increased levels of pro-inflammatory cytokines may give rise to to shock and tissue injuries in the heart, liver and kidneys, as well as pulmonary or multi-organ failure. They also cause widespread lung pathology, causing to substantial infiltration of neutrophils and macrophages, widespread alveolar injury with the development of hyaline membranes and a widespread thickening of the alveolar wall (Figure 1).[12] Spleen atrophy and lymph node necrosis were also detected, suggestive for immune-mediated injury in died cases. Besides the cytokine-based pathology in severe COVID-19 patients, stimulation of complement system has also been reported, showing that complement inhibitors, if utilized at an early stage of the infection, may soothe the inflammatory harm. Cytokine storm causes widespread inflammation of the lung, damage in the other organs and circulatory failure. This supposed cytokine storm can commence viral sepsis and inflammatory-induced pulmonary damage which cause to other complications comprising pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure and, potentially, death. High neutrophil and reduced lymphocyte counts also associate with disease severity and fatality.[3,13,14]

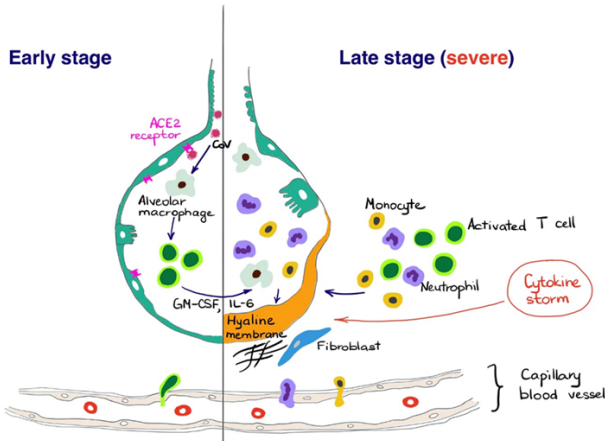

Figure 1 Inflammatory processes occurring in the alveolus of the lung in SARS-CoV-2 infected individuals.[12]

The reflection from immunopathogenesis of COVID-19 into management

SARS-CoV-2 infection can stimulate innate and adaptive immune responses. Nevertheless, uninhibited inflammatory innate responses and weakened adaptive immune responses may direct to both local and systemic tissue injuries. In critical COVID-19 patients, lymphopenia is a frequent characteristic, with considerably decreased numbers of CD4 T cells, CD8 T cells, B cells and natural killer (NK) cells, as well as decreased proportion of monocytes, eosinophils and basophils.[3,11,12]

Citation: Özdemir Ö, Erkun O. Solving puzzle of the immunopathogenesis for management of COVID-19 disease. *MOJ Immunol.* 2020;7(1):13–15. DOI: 10.15406/moji.2020.07.00258

Elevations in neutrophil numbers and in neutrophil-to-lymphocyte proportion are observed in patients with COVID-19.

The demonstration of SARS-CoV-2-specific IgM and IgG in cases helps to diagnose the disease, in association with RT-PCR-based tests. Nonetheless, some investigations analyzing COVID-19 patients indicated that cases with critical disease often had an augmented IgG response and an elevated titer of antibodies, which was found to be related with worse outcome. This was indicative of likely antibody-dependent enhancement (ADE) of SARS-CoV-2 infection.[3,6]

Interestingly, it was demonstrated that a neutralizing monoclonal antibody aiming the receptor-binding domain of the spike protein of the linked MERS virus can augment viral entry.[10] A possible pathogenic outcome of antibodies attacked at SARS-CoV-2 would be of key distress for vaccine progress and antibody-based treatments. Further large-cohort randomized controlled studies are necessary to validate or ignore this risk.

Conclusion

In brief; immune system seems to have an essential role in the pathogenesis of COVID-19 disease. Consequently, reflected from understanding of this role, immunologic therapeutic approaches including use of tocilizumab, plasma therapy,[15] etc. are currently gaining popularity.

Acknowledgments

None.

Conflicts of interest

There is no conflict of interest.

References

1. Özdemir Ö. Coronavirus Disease 2019 (COVID–19): Diagnosis and management (narrative review). Erciyes Med J. 2020; 42(3).
2. Gorbalenya AE, Baker SC, Baric RS et al. The species Severe acute respiratory syndrome–related coronavirus: classifying 2019–nCoV and naming it SARS–CoV–2. *Nat Microbiol.* 2020;5:536–544.
3. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID–19. Viruses. 2020;12(4):372.
4. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–273.
5. Abdulamir AS, Hafidh RR. The possible ımmunological pathways for the variable ımmunopathogenesis of COVID—19 infections among healthy adults, elderly and children. *Electron J Gen Med.* 2020;17(4):em202.
6. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J. (Engl).* 2020.
7. Li W, Moore MJ, Vasilieva N, et al. Angiotensin–converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426(6965):450–454.
8. Zou X, Chen K, Zou J, et al. Single–cell RNA–seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019–nCoV infection. *Front Med.* 2020;14(2):185–192.
9. Lu R, Zhao X, Li J, Niu P, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565–574.
10. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID–19 and potential vaccines: Lesson learned from SARS and MERS epidemic. *Asian Pacific Journal of Allergy and Immunology*. 2020;38(1):1–9.
11. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID–19. *Journal of Pharmaceutical Analysis*. 2020;10(2):102–108.
12. Shi Y, Wang Y, Shao C, et al. COVID–19 infection: the perspectives on immune responses. *Cell Death Differ.* 2020;27:1451–1454.
13. Xu Z, Shi L, Wang Y, Zhang J, et al. Pathological findings of COVID–19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020.
14. Lu X, Zhang L, Du H, et al. SARS–CoV–2 infection in children. *N Engl J Med.* 2020;382:1663-1665.
15. Özdemir Ö, Melek Arsoy HE. Convalescent (immune) plasma therapy with all aspects: yesterday, today and COVID–19. *Erciyes Med J.* 2020;42.