

## Prospects and Opinions in Immunopathogenesis of COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the extreme acute respiratory syndrome. CoVs are enveloped positive-sense RNA nucleic acid viruses characterized by a distinctive replication strategy; they are round and sometimes pleomorphic shapes. COVID-19 is regarding the new genera of coronaviridae that appear the first time in Wuhan, China, in early December 2019.<sup>[1,2]</sup> At present, no specific drug or other therapeutics approved by the FDA, the number of cases due to the novel (COVID-19) presents a serious public health problem worldwide, so deep understanding of immunopathogenesis, effective treatment methods, and more effective management strategies should be discovered as soon as possible to prevent or treat this new virus.<sup>[3]</sup>

The immunopathogenic mechanisms of COVID-19 which cause pneumonia tend to be especially complex. Mutation rates of RNA viruses such as COVID-19 are higher than the DNA viruses, indicating a more effective survival and pathogenesis adaptation.<sup>[4]</sup>

Immunopathogenesis and severity of COVID-19 can be influenced by viral and immune system factors; viral factors include virus type, viral titer, viral load, mutation, and *in vitro* viability of the virus. The individual's immune system factors include physical status, age, nutritional status, gender, neuroendocrine-immune regulation, and genetics (such as human leukocyte antigen [HLA] genes). These factors all determined whether a person is infected with the virus, the re-infection, and the duration and severity of the disease.<sup>[5]</sup>

Many COVID-19 patients have mild-to-moderate symptoms but about 15% progress to extreme pneumonia and about 5% ultimately undergo acute respiratory distress syndrome, septic shock, and/or multiple organ failure.<sup>[6,7]</sup>

The clinical phase of COVID-19 is divided into three: the viremia phase, the acute phase (pneumonia phase), and the recovery phase. If the patient's immune function in the acute time (time of pneumonia) is successful, and no further essential infections, the virus can be successfully blocked, instead join the process of recovery. If the patient is older or immune impaired in combination with other basic diseases such as hypertension and diabetes, the immune system cannot control the virus effectively during the acute phase.<sup>[8]</sup>

COVID-19 infects cells by attaching enzyme-converting angiotensin receptors-II.<sup>[6-9]</sup> Genome codes for at least four major structural proteins: spikes, membranes, envelopes, nucleocapsid proteins, and other accessory proteins that help replicate and facilitate cell entry.<sup>[10]</sup>

Infection with SARS-CoV-2 will activate innate and adaptive immune responses. Unregulated inflammatory innate responses

and impaired adaptive immune responses can, however, result in damage to the tissue locally and systemically.<sup>[11]</sup>

When the virus reaches the cells, it must introduce its receptor to the antigen presentation cells, which is a key part of the body's antiviral immune system. Global histocompatibility complex (HLA in humans) produces antigenic peptides and is then detected by virus-specific cytotoxic T lymphocytes. Therefore, the knowledge of the SARS-CoV-2 antigen presentation should aid our comprehension of COVID-19 pathogenesis.<sup>[5]</sup>

Some of the severe cases of COVID-19 infections admitted to the intensive care unit revealed high levels of pro-inflammatory cytokines, such as interleukin 6 (IL)-2, IL10, IL7, GCSF, IP10, MCP1, MIP1  $\alpha$ , and TNF  $\alpha$ , which are reasoned to begin severity of the disease.<sup>[6]</sup>

It was observed that, in severe cases, most of the damage to lung tissue is due to severe inflammation rather than a direct damaging effect of the virus itself.<sup>[12,13]</sup>

Lymphopenia is a common feature in patients with severe cases but not a mild disease, with drastically reduced numbers of CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells,<sup>[6,13]</sup> besides a decreased percentage of basophils, monocytes, and eosinophils.<sup>[13]</sup>

In addition, markers of exhaustion on cytotoxic lymphocytes such as NKG2A include In COVID-19 patients, NK cells and CD8+ T cells are upregulated. The numbers of CD4 + T cells, CD8+ T cells, B cells, and NK cells, and the markers of exhaustion on cytotoxic lymphocytes normalize in patients who have recovered or are convalescent.<sup>[14]</sup>

Extreme COVID-19 is characterized by pneumonia, lymphopenia, depleted lymphocytes, and a cytokine outbreak. The major development of an antibody is observed; however, whether it is defensive or pathogenic remains to be determined.<sup>[11]</sup>

COVID-19 infection is capable of producing an excessive immune reaction in the host that called a cytokine storm, the effect is extensive tissue destruction. This storm is antagonized by IL-6. It is produced by activated leukocytes and also acts on a wide range of cells other than tissues. It is capable of promoting B lymphocyte differentiation, promoting the growth of certain immune cells and inhibiting the growth of others. It plays a significant role in thermoregulation and also promotes acute phase protein development. While IL-6's key function is pro-inflammatory, it can have anti-inflammatory effects, too. Throughout infectious conditions, allergies, autoimmune disorders, respiratory problems, and certain forms of cancer, IL-6 in effect rises. While IL-6's key function

is pro-inflammatory, it can have anti-inflammatory effects, too. Throughout infectious conditions, allergies, autoimmune disorders, respiratory problems, and certain forms of cancer, IL-6 in effect rises.<sup>[15]</sup>

Cytokines released in the sense of innate immune responses to viral infections are well known to cause the neuroendocrine system to release glucocorticoids and other peptides, which may inhibit immune responses. Viral particles of infectious SARS-CoV-2 were isolated from the gastrointestinal, fecal, and urine samples.<sup>[11]</sup>

The extent of SARS-CoV-2 infections is intermediate between SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infections.<sup>[16]</sup> The envelope plays a key role in the pathogenicity of viruses among structural protein roles since it facilitates viral assembly and release.<sup>[15]</sup>

C-reactive protein and D-dimer are both observed to be abnormally high, as are elevated rates of pro-inflammatory cytokines that cause shock and tissue harm in the different organs such as heart, liver, and kidney, as well as respiratory failure or multiple organ failure.

They also mediate extensive pulmonary pathology, leading to massive neutrophil and macrophage infiltration, diffuse alveolar damage with hyaline membrane formation and diffuse thickening of the alveolar wall. Furthermore, observed was spleen atrophy and lymph node necrosis, which indicates immune-mediated damage in patients who have died.<sup>[11]</sup>

This suggested possible antibody-dependent enhancement (ADE) of the infection with SARS-CoV-2. In multiple viral infections, the immunopathological effects of ADE were detected as an antibody-mediated enhancement of viral entry and activation of a strong inflammatory response. Worryingly, a neutralizing monoclonal antibody attacking the receptor-binding region of the spike protein of the related MERS virus can improve the viral entry. A possible pathogenic impact of SARS-CoV-2 activating antibodies will be of considerable concern for vaccine production and antibody-based therapies. Additional independent large-cohort studies are demanded to substantiate or dismiss this possibility.<sup>[11]</sup>

Some drugs that enhance the immunomodulatory effect of the immune response against COVID 19 have been suggested in some studies such as AmB,<sup>[17]</sup> tamoxifen,<sup>[18]</sup> and itraconazole.<sup>[19-22]</sup> Besides the antiviral effect of these drugs toward many viral infections.

## CONCLUSION

In addition to being important for clinical management, detection, and monitoring of immunopathological changes in COVID-19 patients may provide potential targets for drug development and discovery. More immune-related research is needed to help us understand pathogenesis, guide disease treatment, and improve forecasting.

The development of COVID-19 infection depends on the virus and the immune system. From previous studies drugs

that suppressed the immune system (anti-inflammatory drugs) may be beneficial in high risk patient to decrease flood of cytokine in the lung besides anticoagulant therapy to reduce blood coagulation disorders.

Many of the deadly cases of elderly and poor persons, including comorbidities, can be clarified because their immune system's intrinsic and adaptive systems are suboptimal. While we recognize that children and elderly people have suboptimal immunity, the problem is why it is serious in the aged, and if any, little signs in infants?

Defining immunopathological changes in COVID-19 patients provides potential targets for drug discovery and is important for clinical management, so we hypothesize that detection of IL-6 is very important in detecting the severity of infection, as well as preventing it from rising high levels leads to severe tissue damage.

Drugs that used for other non-viruses pathogens could be evaluated especially those have the immunomodulatory effect that enhances immune response to produce special immune component like interferons that inhibit COVID-19, especially in immunocompromised and high-risk factors persons.

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## Conflicts of interest

There are no conflicts of interest.

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