Study in SARS-CoV2 infected mice may lay the groundwork for novel therapies to reduce the severity of COVID-19

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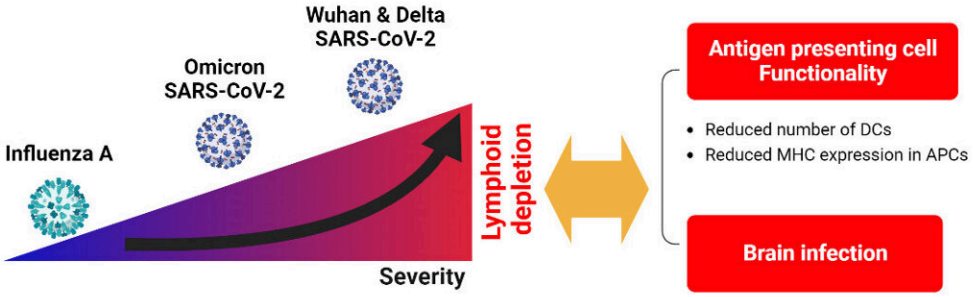

The results collectively demonstrate that lymphoid depletion lesions observed in the spleen serve as a crucial factor reflecting mortality rates. Lymphoid depletion accompanied by reduced APC function was a specific feature observed in the Wuhan and Delta types of SARS-CoV-2 but not in other infections such as Omicron and influenza A and had the greatest prognostic value for disease severity in mice infected with the Wuhan and Delta variants. DCs, dendritic cells; MHC, major histocompatibility complex; APCs, antigen presenting cells. Credit: *The American Journal of Pathology*

Individuals who are immunocompromised are considered at higher risk for severe or longer disease with COVID-19. Understanding the

systemic immune response is vital for research efforts to reduce its effects on multiple organs.

A new study in SARS-CoV2-infected mice reported in *The American Journal of Pathology* found lymphoid depletion lesions in the spleen that may form the groundwork for novel therapies to restore defective antigen-presenting cell (APC) functions in humans to trigger the cellular immune response and potentially reduce the severity of COVID-19.

The severity of COVID-19 varies considerably from no symptoms at all to severe disease with fatal complications. The risk of developing severe disease has been associated with dysregulated immune responses in patients. COVID-19 is known to impact not only the lungs but also non-target organs, leading to long-term complications and, in severe cases, multi-organ dysfunction. In particular, lymphopenia and lymphoid depletion in lymphoid tissues has been associated with poor disease outcomes.

Lead investigators Je Kyung Seong, DVM, Ph.D., Korea Mouse Phenotyping Center (KMPC), Seoul National University, and Jun Won Park, DVM, Ph.D., College of Biomedical Science, Kangwon National University, explained, "The mechanisms involved in the development of severe disease remain elusive, partially due to the limitations in evaluating immunologic factors of clinical samples, which could be affected by various circumstances, such as underlying diseases, age, sex, exposed environments, and eating habits."

They added, "Investigating the factors underlying the risk of developing severe disease in terms of immunodynamics under well-controlled infectious conditions based on animal models is essential to understanding the mortality and immunologic factors that contribute to disease severity. Therefore, gaining insight into the systemic immune response, beyond just the lung-related lesions, is vital for research

efforts focused on reducing the effects of COVID-19 on multiple organs and lessening the long-term consequences."

In this study, human angiotensin-converting enzyme 2 (K18-hACE2) transgenic mouse models susceptible to SARS-CoV-2 infection, the strain of coronavirus that causes COVID-19, were used to investigate the characteristics and determinants of lethality associated with the lymphoid depletion observed in COVID-19.

Dr. Seong noted, "The K18-hACE2 mouse model is extensively employed in preclinical trials for the development of COVID-19 treatments and vaccines. Our research group has performed numerous preclinical studies using this model. During these experiments, we discovered a strong correlation between the mice's mortality rate, fatal brain infections, and lymphoid depletion observed in their spleens."

Dr. Park added, "As similar splenic lesions are also found in patients with severe COVID-19, it is crucial to characterize lymphoid depletion in this lethal mouse model. Doing so will enable a better understanding of the factors contributing to COVID-19 patient mortality and aid in the development of effective therapies to mitigate these outcomes."

The infected mice exhibited a diverse range of disease severity in terms of weight, temperature, lung pathology, spleen pathology, and brain infection. The correlation between these parameters was then analyzed to define the lethality induced by COVID-19 in the mouse model. The results indicated that, in addition to lung lesions, brain viral load is a major determinant of mortality in this mouse model.

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but not in other infections such as Omicron and influenza A and had the greatest prognostic value for disease severity in mice infected with the Wuhan and Delta variants.

Dr. Seong commented, "Thus, we demonstrated that lymphoid depletion associated with suppressed APC function characterizes the lethality of COVID-19 in mouse models."

Dr. Park observed, "Our study may form the groundwork for novel therapies to restore defective APC functions in patients with COVID-19 and possibly prevent its severe progression by enhancing APC functionality."

Accordingly, the investigators recommend evaluating the spleen in K18-hACE2 mice to assess vaccine and therapeutic efficacy in preclinical testing.

More information: Yu Jin Lee et al, Murine Coronavirus Disease 2019 Lethality Is Characterized by Lymphoid Depletion Associated with Suppressed Antigen-Presenting Cell Functionality, *The American Journal of Pathology* (2023). DOI: 10.1016/j.ajpath.2023.03.008

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