INFECTIOUS DISEASE

Targeting the eicosanoid pathway treats COVID-19 in middle-aged mice

Wong, L-Y.R., Zheng. J. et al. *Nature* (2022) https://doi.org/10.1038/s41586-022-04630-3

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 infection is particularly severe in older individuals. Although the developed vaccines are effective, the emergence of new and highly transmissible variants impacts their efficacy. Using a new mouse-adapted SARS-CoV-2 that causes severe disease in middle-aged mice, a study in *Nature* shows that blocking eicosanoid signaling protects mice from lethal infection, opening new avenues for future therapeutics.

"Our goal was to isolate a virus that caused severe disease in all strains of mice and would be useful for investigating the pathogenesis of severe COVID-19, as occurs in patients who are hospitalized," explain Lok-Yin Roy Wong and Stanley Perlman, first and last author of the study, respectively. SARS-CoV-2 relies on the cellular receptor angiotensin-converting enzyme 2 (ACE2) to enter a host cell and cannot infect mice due to an incompatibility between the spike (S) protein of the virus and the mouse ACE2. To overcome this impediment, Wong, Zheng et al. generated a mouse-adapted SARS-CoV-2 via mutagenesis of the SARS-CoV-2 genome and serial passaging of the virus in mice. Several mutations in the S protein of the new mouse-adapted virus were similar to those observed in variants of concern in humans.

The researchers used the mouse-adapted virus to investigate the role of an eicosanoid pathway, involving the prostaglandin D2 (PGD2), its receptor PTGDR (or DP-1), and the phospholipase A2 group 2D (PLA2G2D) on severe pathology after SARS-CoV-2 infection. Previous work from the team showed that infection with SARS-CoV, another pathogenic human coronavirus, induced an age-dependent increase in disease severity that was attributed to increased PLA2G2D/PGD2/DP-1 activity. Here, the researchers show that knocking-out *PLA2G2D* and *PTGDR* in middle-aged SARS-CoV-2 infected C57BL/6 mice completely or partially prevented lethality; asapiprant, a PTGDR antagonist, also prevented SARS-CoV-2-induced mortality. Altogether, these results highlight the critical role of the PLA2G2D/PGD2/DP-1 pathway in COVID-19 pathology and identify asapiprant as a novel potential treatment for COVID-19.

The researchers are planning to continue this work by elucidating how the changes observed in the mouse-adapted virus increase its virulence, investigating the mechanisms of action of asapiprant and using the virus for studying long COVID-19. "We are also awaiting the results of clinical trials that are examining whether asapiprant will be useful for the treatment of hospitalized patients with severe COVID-19.", further comment Wong and Perlman.

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