INFECTIOUS DISEASE

Humanized mice for COVID-19 research

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Although extensive research has been conducted to understand and treat COVID-19, the detailed mechanisms underpinning severe disease are not well understood. Therefore, the development of appropriate animal models that recapitulate human clinical features and immune responses following SARS-CoV-2 infection is critical. In *Nature Biotechnology*, researchers in the lab of Richard Flavell at Yale University describe a new humanized mouse model of SARS-CoV-2 infection that recapitulates severe COVID-19.

The research team used an adeno-associated virus vector to deliver human ACE2 to the lungs of immune-reconstituted MISTRG6 mice transplanted with human hematopoietic stem and progenitor cells (HSPCs). These mice have an immune system similar to humans, including a complete human monocyte and macrophage compartment.

Intranasal inoculation of SARS-CoV-2 in MISTRG6-hACE2 mice resulted in high level of viral infection in the lungs for at least 35 days post-infection (dpi), chronic weight loss and severe lung pathology with pulmonary fibrosis. In the report, Sefik and colleagues explain that these features are unique to MISTRG6 mice with human immune cells and hACE2 expression, and have not been observed in previous animal models of COVID-19, including virally transduced ACE2 mice and ACE2 transgenic mice, which suggests that human immune cells uniquely contribute to severe pathology and/or viral RNA persistence. SARS-CoV-2 infection induced aberrant macrophage response in the lungs of MISTRG6-hACE2 mice and recapitulated T and B cell responses induced by SARS-CoV-2 infection in patients. Gene expression analysis revealed that SARS-CoV-2 infection promoted a persistent interferon-stimulated gene signature in the lungs of the humanized mice, a phenotype also identified in patients with COVID-19.

Next, the investigators evaluated the effects of human monoclonal recombinant antibodies (mAb) and dexamethasone in this mouse model of chronic COVID-19. Both treatments could help treat COVID-19 in the mice, but mAbs were only effective if administered early in the disease, whereas steroids were only effective at later stages of the disease. These results suggest that the same inflammatory macrophages are involved in the early protective anti-viral response and the subsequent pathological immune response. "Separating the two aspects of the immune response—infectious viral clearance and immunopathology—recapitulated in our model might prove useful in the control of COVID-19. Patients might benefit from early mAb treatment coupled with dexamethasone later in infection," write the investigators.

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