

INFECTIOUS DISEASE

Genetically diverse mice to model variable responses to SARS-CoV-2 infection

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The symptoms of COVID-19 vary widely from one person to another. While some individuals are asymptomatic following SARS-CoV-2 infection, others develop severe forms of the disease. Identifying the risk factors that influence COVID-19 disease could guide the development of more personalized therapies. In a new study published in *Nature Communications*, researchers used mice with different genetic backgrounds to assess the impact of host genetics on immune responses and COVID-19 severity.

The K18-hACE2 mouse model, in which human angiotensin-converting enzyme 2 (hACE2) expression is driven by the K18 promoter in C57BL/6 mice, is currently one of the most commonly used mouse models for SARS-CoV-2 investigations. “While the model was effective for testing vaccines and anti-viral treatments, the rapid time course and severity of infection, as well as other aspects of the response, did not accurately represent the broad spectrum of clinical profiles

emerging in infected human populations,” explains Nadia Rosenthal, senior investigator on the study.

Rosenthal’s team reasoned that the fastest way to develop new COVID-19 models with variable responses to SARS-CoV-2 infection was to cross the available K18-hACE2 transgenic mouse with a panel of genetically distinct inbred mouse strains. The JAX investigators teamed up with Sonja Best and her colleagues at the Rocky Mountain Laboratories to infect the hybrid offspring with SARS-CoV-2 and study the response to infection. “In a matter of weeks, we knew our intuition had paid off: the new models displayed a wide variety of responses from asymptomatic to severe,” comments Rosenthal.

Next, the researchers carried out a detailed analysis of the inflammation induced by SARS-CoV-2 infection, which revealed that mouse hybrids that were highly resistant to disease rapidly launched a robust type I interferon (IFN-I) response, a phenomenon not observed in the original

hACE2 model. Blocking IFN-I signaling prior to infection did not render resistant hybrids as susceptible to infection as the original hACE2 mice, indicating that IFN-I is not solely required for the control of virus clearance and dissemination. Regulated proinflammatory responses were also required for control of SARS-CoV-2 replication in resistant mice.

Rosenthal explains that further studies on these mice could help predict inflammatory responses in patients based on underlying genetic features, adding that these models could also be useful to study other infectious diseases. “We are currently contemplating new approaches to pandemic preparedness, involving the preselection of genetically diverse mouse strains with varied responses to additional viral groups and other pathogens,” she concludes.

Alexandra Le Bras

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