EDITORIAL

The Decision to Publish Gutierrez-Alvarez et al., "Middle East Respiratory Syndrome Coronavirus Gene 5 Modulates Pathogenesis in Mice"

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The paper "Middle East respiratory syndrome coronavirus Gene 5 modulates pathogenesis in mice" by Gutierrez-Alvarez et al., in this issue of the *Journal of Virology* (1), demonstrates that the MERS-CoV accessory protein, Gene 5, also known as ORF5, plays a major role in MERS-CoV pathogenesis. While constructing and characterizing a cDNA clone of a mouse-adapted strain of MERS-CoV, the investigators noted that their mouse-adapted virus (MERS-MA) contained an early stop codon and deletions within the viral Gene 5. Gene 5 is a viral accessory gene that is dispensable for viral replication, and while prior studies indicated that Gene 5 modulates host inflammatory responses (2), a function for Gene 5 in MERS-CoV pathogenesis is incompletely understood. Therefore, Gutierrez-Alvarez et al. constructed a cDNA clone of MERS-MA carrying a complete deletion of the Gene 5 (MERS-MA-Δ5) and characterized this virus for the capacity to cause disease in mice. Somewhat surprisingly, they discovered that the MERS-MA-Δ5 virus displayed enhanced virulence in mice, including increased respiratory pathology at late times postinoculation, as well as higher mortality compared with the parental MERS-MA virus. Further analysis indicated that the MERS-MA-Δ5 virus-infected mice exhibited delayed type I interferon (IFN) and inflammatory responses in the lung, suggesting that Gene 5 modulates the host type I IFN response and suppresses MERS-CoV-induced pathology in the lungs.

While this study of MERS-MA-Δ5 virus in mice raises concerns about altering the virulence of a potential pandemic pathogen (PPP), these concerns are balanced by the fact that the results provide several significant advances for the field. Our understanding of a role for Gene 5 in MERS-CoV pathogenesis is incomplete, and the work of Gutierrez-Alvarez et al. provides intriguing new insights into Gene 5 function and its potential role in MERS-CoV pathogenesis in susceptible hosts. Furthermore, Gene 5's role in suppressing respiratory pathology and disease

may have relevance for understanding how MERS-CoV interacts with its natural hosts. Bats, which are thought to serve as a natural MERS-CoV reservoir, mount dampened inflammatory responses to MERS-CoV (3). While this is largely due to the unique nature of the bat innate immune system, it also raises the possibility that Gene 5 may limit MERS-CoV pathogenesis in its natural host and promote viral maintenance. There also is a growing body of evidence that host inflammatory responses contribute to the respiratory pathology induced by MERS-CoV, SARS-CoV, and SARS-CoV-2, and targeting these responses has potential therapeutic benefit. This raises the possibility of comparing the host response of unmodified MERS-CoV and the MERS-MA-Δ5 mutant to identify targets for therapeutic intervention. Therefore, while the MERS-MA-Δ5 virus does raise PPP concerns, it also is important to consider the significant scientific value provided by this study's findings on Gene 5's role in MERS-CoV pathogenesis.

Like all other papers considered for publication by the *Journal of Virology*, reviewers were asked to evaluate the paper for novelty, scientific rigor, and significance and to consider whether the research represented dual use research of concern (DURC). The manuscript also was evaluated for DURC by members of the Responsible Publication Committee of the American Society for Microbiology, which publishes the *Journal of Virology*. The committee concluded that communicating new information about the pathogenesis of virulent coronaviruses with the potential to illuminate new therapeutic targets outweighed potential risks, and ASM decided to move forward with publication.

Given the threat to human health posed by highly pathogenic coronaviruses and the paucity of countermeasures available, we think that research on these viruses is important. We support efforts in the coronavirus research community to conduct this work to answer the most important scientific questions in the safest possible manner.

REFERENCES

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