ABSTRACT

Mouse model of human coronavirus (HCoV)-NL63: comparison with rhinovirus-(RV)-A1B and effects of prior RV infection

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Introduction: HCoV-NL63 is one of seven coronaviruses which cause respiratory infections in humans. While HCoV-NL63 usually causes minor respiratory symptoms, there is evidence that it can cause asthma exacerbations through angiotensin-converting enzyme 2 (ACE2) as a receptor; similar to SARS-CoV-2. We sought to establish a mouse model of HCoV-NL63, compare with an established model of RV-A1B, and determine the effect of prior RV-A1B infection on HCoV-NL63 replication.

METHODS AND RESULTS

Figure 1. HCoV-NL63 induces lung inflammation in K18-ACE2 mice. LLC-MK2 cells infected with wild type (left panel) or HCoV-NL63 (right) (fold GAPDH). 1. 0 2 3 5 day post-infection.

SUMMARY AND CONCLUSIONS

• We established a mouse model of HCoV-NL63 using mice expressing human ACE2 under control of the keratin 19 promoter. Compared to wild type mice, HACE2 mice showed significantly higher levels of HCoV-NL63 RNA and nsp3, a non-structural viral protein that is produced in replicating virus. In addition, HCoV-NL63-infected HACE2 mice showed increased BAL neutrophils and lymphocytes, as well as peribronchial and perivascular infiltrates compared to mock-infected controls. Together these data suggest that HCoV-NL63 causes a replicative infection in HACE2 transgenic mice. Our work provides a BSL-2 animal model to study CoV infection in mice.

• We also found that prior RV-A1B infection significantly reduced HCoV-NL63 replication and viral-induced pulmonary inflammation, an example of viral interference. However, in our model, we did not find evidence that RV-A1B interferes with HCoV-NL63 infection by enhancing IFN production.

• Finally, we found that mRNA expression of many pro-inflammatory genes was significantly higher after RV-A1B infection than HCoV-NL63 infection, including TLR2, TLR4, IFN-α, IFN-β, IFN-γ, IL-6, CCL4, CXCL10, CCL2, and CCL3. In contrast, the interferon-stimulated genes (ISGs) and nsp3 were downregulated.

• These findings support the hypothesis that HCoV-NL63 infection with or without viral interference by RV-A1B infection may provide insight into the mechanisms underlying HCoV-induced asthma exacerbations and viral interference.