Rapid Reviews COVID-19

Review 2: "Nasally-delivered interferon- λ protects mice against upper and lower respiratory tract infection of SARS-CoV-2 variants including Omicron"

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RR:C19 Evidence Scale rating by reviewer:

- **Strong.** The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

The manuscript by Z. Chong et al. describes the effects of interferon-lambda (IFN-L) on viral burden, weight loss, lung histology, and lung RNA expression in mouse models of SARS-CoV2 infection. IFN-L administration was shown previously to reduce viral burden and mortality caused by SARS-CoV-2 infection in mouse models. In this paper, the authors extend these studies and use both mouse-adapted viruses in conventional 129 mice, and beta and omicron viral variants in mice transgenic for huACE2 receptor to show IFN-L intranasal pretreatment reduces morbidity as measured by body weight, viral burden, and lung histology. Cytokine gene expression was significantly reduced in infected lungs following intranasal IFN-L treatment, coordinate with the reduction in inflammation. To identify cells in infected lungs responsible for the production of endogenous IFN-L, the authors FACS sorted epithelial cells, macrophages, monocytes, T cells, B cells, and dendritic cells, and measured IFN-L RNA transcripts. Epithelial and dendritic cells produced the highest IFN-L expression, and these cells and neutrophils expressed the IFN-L receptor, consistent with other studies. Transgenic knockout mice for Mavs, cGas, and Myd88 were used to show that the SARS-CoV-2 virus is recognized by RNA sensing of Mavs and Myd88 pathways to induce IFN-L genes. Bone marrow chimeras with wt and IFN-L receptor knockout mice showed that IFN-L signaling in lungs, not hematopoietic cells, is critical for the reduction in viral burden. The experiments are informative and of general interest to innate immunity and respiratory infections, specifically for SARS-CoV-2, and provide data on the prophylactic value of IFN-L.

Comments:

1. Although weight loss and viral respiratory burden are measured, the mortality caused by SARS-CoV2 infection is not addressed. What is the mortality with the viral doses selected and what effect does IFN-L have on animal survival in their systems?

2. The title and description state that IFN-L protects mice from infection. The term protect is vague, and specific effects tested could be used such as reduction in viral burden and/or inflammation.
3. There are clear changes in cytokine expression following infection with or without IFN-L pretreatment. How do these values compare to uninfected basal levels?
4. The summary mentions radio-resistant cells. This should be clarified to specify the results of bone chimera experiments.