Review 1: "Omicron-induced interferon signalling prevents influenza A virus infection"

Dennis Metzger¹ Tarani Kanta Barman²

¹Albany Medical College Immunology and Microbial Disease UNITED STATES,
²Research Scientist-II Department of Pathology Galveston National Laboratory University of Texas Medical Branch Galveston, Texas

Published on: Oct 30, 2022

DOI: https://doi.org/10.1162/2e3983f5.cfae9dcd

License: Creative Commons Attribution 4.0 International License (CC-BY 4.0)
**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:**

In this study, the authors demonstrated that infection of human primary cell cultures with the SARS-CoV-2 Omicron variant induced a significant amount of biologically active type I and type III interferon, while infection with the Delta variant did not induce interferon responses. This correlated with the ability of SARS-CoV-2 Omicron infection, but not Delta infection, to protect the cell cultures from subsequent influenza A virus co-infection. The study design, methodology, and data analysis were all performed in a scientifically sound manner and the results are convincing.

An important point is that the study was conducted using human primary cell cultures, which increases its clinical relevance. Also, the authors indicate in Supplementary Figure 3 that in the human population, when Delta was the primary circulating SARS-CoV-2 variant of concern, influenza cases surged after restrictions were lifted, while after the Omicron variant became prevalent, the number of influenza-like illnesses strongly declined. These facts further increase the manuscript’s clinical relevance. However, all experiments were conducted using only an in vitro cell culture system and there were no in vivo animal studies to validate the findings. This is a major limitation of the study, which, to their credit, the authors clearly acknowledge in the Discussion.

In the whole animal, it is possible that other cytokines could be differentially induced by Delta versus Omicron infection, and at various times after infection, such that these additional cytokines could impact susceptibility to subsequent influenza disease. Similarly, the cytokines that are induced during in vivo infection, including interferon, could act on cells other than those examined in this manuscript (epithelia and monocytes); such cells could significantly influence resistance to influenza co-infection. Despite these concerns, the manuscript represents a scientifically rigorous and highly novel study that will inform future investigations.