Rapid Reviews COVID-19 •

Review 3: "A Prenylated dsRNA Sensor Protects Against Severe COVID-19 and is Absent in Horseshoe Bats"

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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:

In this manuscript, Wickenhagen et al. perform a screen to identify interferon-stimulated genes that inhibit SARS-CoV-2 replication. They show that the dsRNA sensor, OAS1, potentially inhibits SARS-CoV-2 replication dependent on the expression of the antiviral endoribonuclease, RNase L. Moreover, the authors identify an intronic SNP (Rs10774671) in OAS1 that regulates the inclusion of a CAAX prenylation site motif (p46 isoform), which is required for OAS1-mediated inhibition of SARS-CoV-2 replication. The authors show that the p46 prenylated OAS1 isoform specifically antagonizes viruses that replicate within replication organelles, leading to a model whereby membrane-bound prenylated OAS1 senses SARS-CoV-2 in replication organelles and activates RNase L-mediated decay of host and/or viral RNAs to reduce viral replication.

Importantly, the authors show that the p46 prenylated OAS1 isoform was associated with protection from severe COVID-19 in hospitalized patients. Lastly, the authors show that the bat species that are the presumed source of SARS-CoV-2 lack the p46 prenylated OAS1 isoform. Thus, SARS-CoV-2 did not have to contend with the OAS1/RNase L pathway. This potentially explains why SARS-CoV-2 does not encode mechanisms that other coronaviruses use to evade the OAS1/RNase L pathway, such as phosphodiesterases that cleave the 2'-5' oligoadenosine-signaling molecule produced by OAS1. This provides an explanation for why SARS-CoV-2 is sensitive to the OAS1/RNase L pathway.

Overall, the authors present data that strongly support their conclusions. An important implication of this work is that SARS-CoV-2 could evolve, possibly by recombination with other human coronaviruses that encode phosphodiesterases that block the RNase L defense pathway and thereby become more pathogenic. One weakness in this paper is the lack of data directly showing that the p46 isoform is prenylated and is

incorporated into the membrane. While the authors' mutational analyses of the CAAX prenylation site motif suggest that the amino acids in this motif are important for the anti-SARS-CoV-2 activity of OAS1, the authors do not present additional evidence that this protein is prenylated. Several experimental approaches could directly demonstrate that the p46 OAS1 isoform is prenylated at the CAAX motif. For example, the authors could measure incorporation of OAS1, with or without the CAAX motif, in cytosolic and membrane-bound fractions via western blotting. Showing direct evidence that the p46 OAS1 isoform is prenylated, and that this isoform incorporates into membranes, would strengthen their primary model.