Rapid Reviews COVID-19 •

Review 2: "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:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

This manuscript suggests that the innate immunity protein, OAS1, protects humans from severe COVID-19.

OAS1 has been studied for multiple decades. It is a well-known component of the antiviral interferon (IFN) system. Nevertheless, the current paper stands out as providing a remarkably strong example of antiviral OAS1 activity in cells. Adding to the intrigue, this antiviral activity is attributed to a specific isoform of OAS1, which may help us understand the perplexing variety of OAS gene variants and OAS isoforms that are found in vertebrate genomes.

The basic design of the work, leading the authors to pinpoint OAS1, is a functional screen for anti-SARS-CoV-2 activity among IFN response effector genes. The screen is rather creative due to the use of an IFN response-deficient cell background. This background allows the authors to track antiviral effects of individual antiviral genes, separate from pleiotropic effects of other genes acting in IFN responses.

OAS1 emerged from this screen as a suppressor of SARS-CoV-2, capable of attenuating viral titers in cells by greater than 1,000-fold. The authors show that, as expected, OAS1 achieves this activity via RNase L, a known antiviral receptor working in tandem with OAS1.

The authors further refine the study by demonstrating that the anti-SARS-CoV-2 activity of OAS1 is critically dependent on the presence of a post-translational modification—a hydrophobic lipid anchor (prenylation). Prenylation has to be present in order for OAS1 to block the SARS-CoV-2 virus, which marks isoform p46 of OAS1 (encoding prenylation site) as a specific OAS1 form engaged in anti-SARS-CoV-2 defense. The authors show that prenylation locates OAS1 to ER-like structures, likely via membrane association. Thus, OAS1 is targeted to endomembranous structures,

which likely serve for SARS-COV-2 replication, where OAS1 p46 must bind its cognate ligand (viral dsRNA) to activate RNase L and to achieve the antiviral effect.

The manuscript has a few shortcomings that stand out. There are some formatting issues, such as a missing Supplementary Figure S3.

Further, the authors identify the OAS1 p46 isoform as a major anti-SARS-CoV-2 factor, yet the expression level of this isoform has no effect on disease severity (Fig. 5D right panel). This lack of protection is counter-intuitive.

Fig. 5D left panel: the authors report ~100-fold stronger median expression of OAS1 p46 isoforms in patients with a less severe COVID-19. Considering that OAS1 is an ISG, this 100-fold difference could arise from a difference in IFN response status rather than specifically from OAS1 p46. Higher OAS1 levels could reflect a stronger general IFN response in these patients, hence milder COVID-19. To test for this, one could re-plot Fig. 5D for p42 isoform or other ISGs, such as OAS2 and OASL. If data for other ISGs resemble the current Fig. 5D, IFN response differences could indeed be the main cause underlying different disease severity.

Overall, this is an interesting study, with the potential to considerably advance our understanding of immune defenses from COVID-19, antiviral effector genes, and the OAS/RNase L system specifically.