Review of: "USP22 controls type III interferon signaling and SARS-CoV-2 infection through activation of STING"

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In this manuscript, Karlowitz et al. report that USP22 functions as a negative regulator of basal ISG expression, JAK/STAT activation and IFN signaling without the exogenous IFNs or viral infection. USP22 controls basal and 2'3'-cGAMP-induced STING ubiquitination, phosphorylation and activation, and combined loss of USP22 and STING rescues ISG expression, STAT signaling and IFN-λ production. Additionally, the authors identify USP22 as crucial host factor in shaping SARS-CoV-2 antiviral defense by priming cellular anti-viral responsiveness prior to virus infection. Overall, this manuscript defined an impressive function of USP22 in the regulation of IFN signaling and the mechanisms are adequately addressed. Two major concerns as below:

1. The major concern is that some articles, e.g. Cai, Z. et JEM 10.1084/jem.20191174, report the positive role of USP22 in regulating IFNs, which seems to be controversial to this manuscript. Although the work focused on the basal effect of USP22, but USP22 also exhibited as a negative regulator for IFNs with ISD stimulation. This point requires clarification and explanation.

2. The change of Sting protein expression after USP22 KO is less than two-fold (Figure 5D). However, the change of IFN in Figure 5B is much larger than two-fold. It is hard to attribute the phenomenon of the change of IFNs to the effect of USP22 on Sting at this stage. The authors should give some explanation.