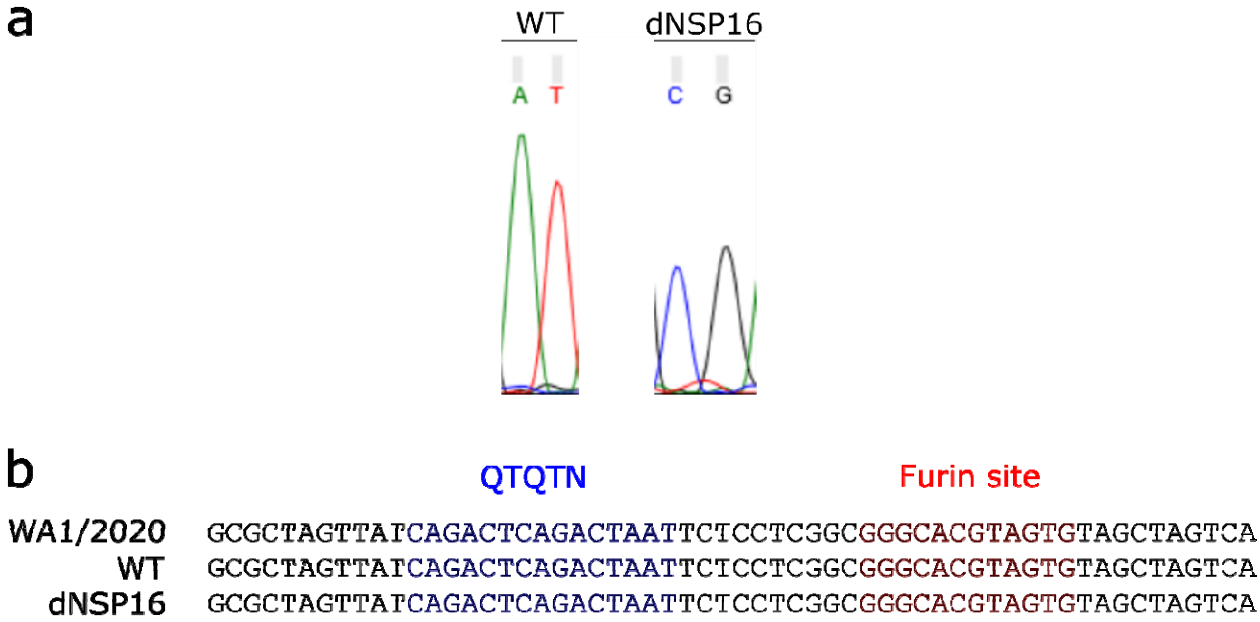


Figure S1. D130 mutation is stable in rescued dNSP16, and rescued infectious clone stocks maintain sequence around furin cleavage site. Viral RNA was extracted from the viral stocks used in the study ("WT" and "dNSP16"). Viral RNA was reverse-transcribed, PCR-amplified around the site of interest, and Sanger sequenced. (a) Shown are the sequencing traces of the 2-base pair site within codon 130 of NSP16 that was mutated from AT to CG to engineer dNSP16. (b) Validated sequence around the furin cleavage site, including the QTQTN motif, for WT and dNSP16, compared to the published sequence for WA1/2020.

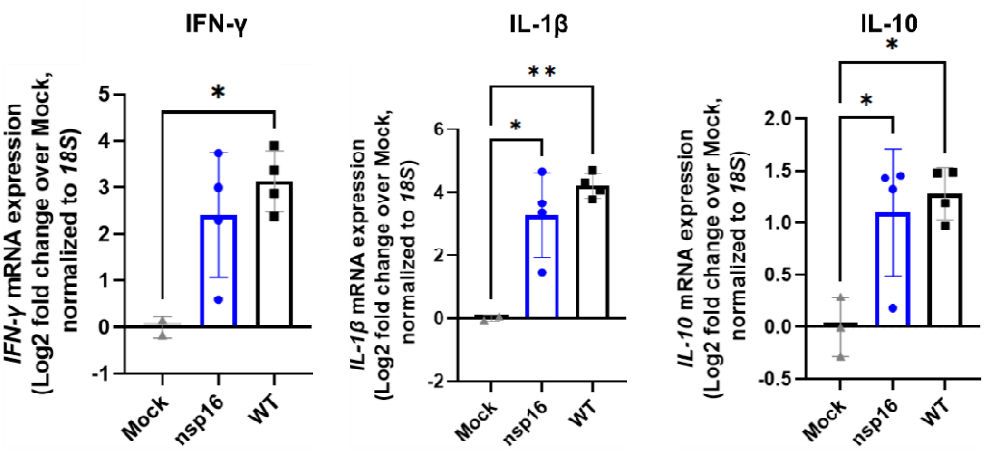


Figure S2. dNSP16 does not drive increased immune gene expression relative to WT. Fold change (log_2) of expression of the indicated immune genes from lung samples isolated from hamsters infected with the indicated virus (or mock), 2 days post-infection. For each panel, fold changes from dNSP16 or WT samples are measured relative to mock samples. Values from individual hamsters are plotted (symbols) as well as means (bars). Error bars denote standard deviation. All samples were normalized to 18S expression, used as a reference. *p<0.05, **p<0.01, *p<0.005, ****p<0.001: results of one-way ANOVA with Tukey's multiple comparison test (α = 0.05).

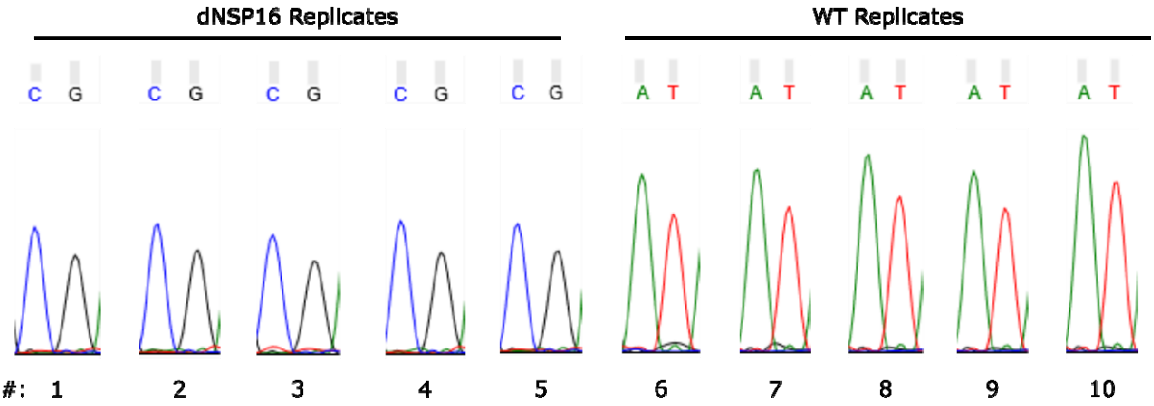
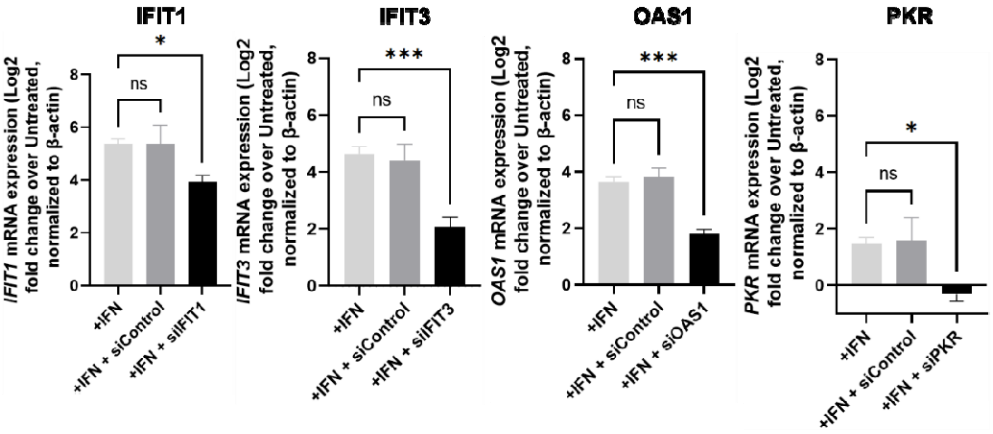


Figure S3. No evidence of reversion of dNSP16 mutation was detected *in vivo*. Viral RNA was extracted from the lungs of hamsters infected with either dNSP16 or WT (numbered 1 through 5 for each group) and which were sacrificed at 4 days post-infection. Viral RNA was reverse-transcribed, PCR-amplified around the site of mutation, and Sanger sequenced. Shown are the sequencing traces of the 2-base pair site within codon 130 of NSP16 that was mutated from AT to CG to engineer dNSP16.



761

762 **Figure S4. Validation of knockdown of immune gene targets in Vero E6 cells**. 1.25 x 10^5 Vero E6 cells/well were reverse
763 transfected with 1 pmol of the control or gene-specific siRNA 2 days prior to harvest and also treated with 100 U IFN-I one day prior
764 to harvest and assessment of gene expression. Fold change (log_2) of gene expression is measured relative to untreated samples
765 (i.e. no IFN-I). All samples were normalized to *β*-actin, used as a reference. *p<0.05, ***p<0.005, ns = not significant: results of
766 one-way ANOVA with Tukey's multiple comparison test (α = 0.05). Means are plotted with error bars denoting standard deviation. n
767 = 3 biological replicates.

768

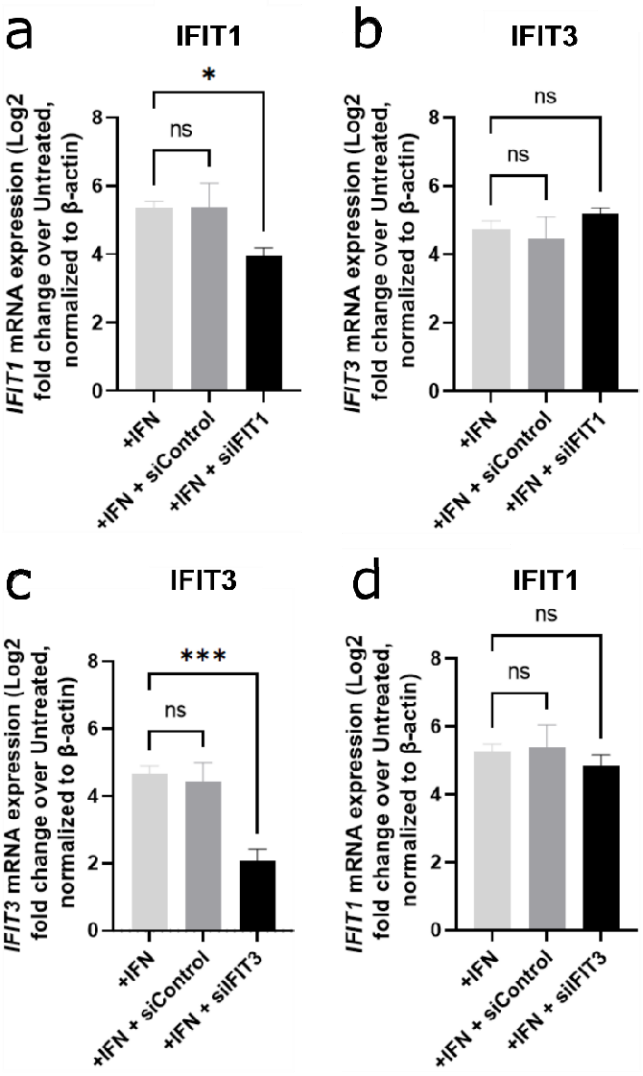


Figure S5. Knockdown of either *IFIT1* or *IFIT3* is specific. 1.25 x 10^5 Vero E6 cells/well were reverse transfected with 1 pmol/well of either a non-targeting siRNA ("siControl") or with an *IFIT1*- (a, b) or *IFIT3*- (c, d) targeting siRNA ("siIFIT1" or "siIFIT3", respectively), or were seeded without treatment. One day later, cells were treated with 100 U of IFN-I to induce interferon-stimulated genes. The following day, cells were lysed for RNA purification and mRNA quantification via reverse transcription and quantitative polymerase chain reaction (PCR). For all panels, gene expression is normalized to *β*-actin (used as a reference), and fold changes are given relative to untreated controls (i.e. no IFN). **p*<0.05, ****p*<0.005, ns = not significant: results of one-way ANOVA with Tukey's multiple comparison test (α = 0.05). Means are plotted with error bars denoting standard deviation. *n* = 3 biological replicates.