

Expanded View Figures

Figure EV1. CRISPR-based gene inactivation efficiently reduces protein product abundance and demonstrates mostly IFN-dependent antiviral activity of ZAP, IFIT3, and IFIT1 together.

- A Western blot showing reduced protein abundance in CRISPR-targeted cells from Fig 3A. Red asterisks denote long (**) and short (*) isoforms of ZAP.
- B Western blot showing reduced protein abundance in CRISPR-targeted cells from Fig 3B. Red asterisks denote long (**) and short (*) isoforms of ZAP.
- C Western blot showing reduced protein abundance in CRISPR-targeted cells from Fig 3C. Red asterisks denote long (**) and short (*) isoforms of ZAP.
- D (Top) Infection of CRISPR-targeted U-2 OS (left, top) or Huh7.5 cells (right, top) that were infected with an MOI of 1 VEEV-GFP (5 h for U-2 OS and 4.5 h for Huh7.5) with and without pretreatment of IFN β (24-h treatment, 20 U/ml for U-2 OS and 100 U/ml for Huh7.5 cells). Graphs represent the mean with error bars representing standard deviation. $n = 3$ biological replicates, one-way ANOVA with Dunnett's test. $^{ns}P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. (Bottom) Western blot of ISG20 from lysates of "quadruple-targeted" U-2 OS (left, bottom) or Huh7.5 cells (right, bottom) with and without pretreatment of IFN β (24-h treatment, 20 U/ml for U-2 OS and 100 U/ml for Huh7.5 cells).
- E Western blot from lysates of U-2 OS cells after 5-h infection with VEEV-GFP or IFN β treatment (20 U/ml for 24 h). Red asterisks denote long (**) and short (*) isoforms of ZAP.
- F Western blot from lysates of U-2 OS CRISPR-targeted or control cells after 24-h treatment 500 ng/ml of IFN λ . Red asterisks denote long (**) and short (*) isoforms of ZAP.

Source data are available online for this figure.

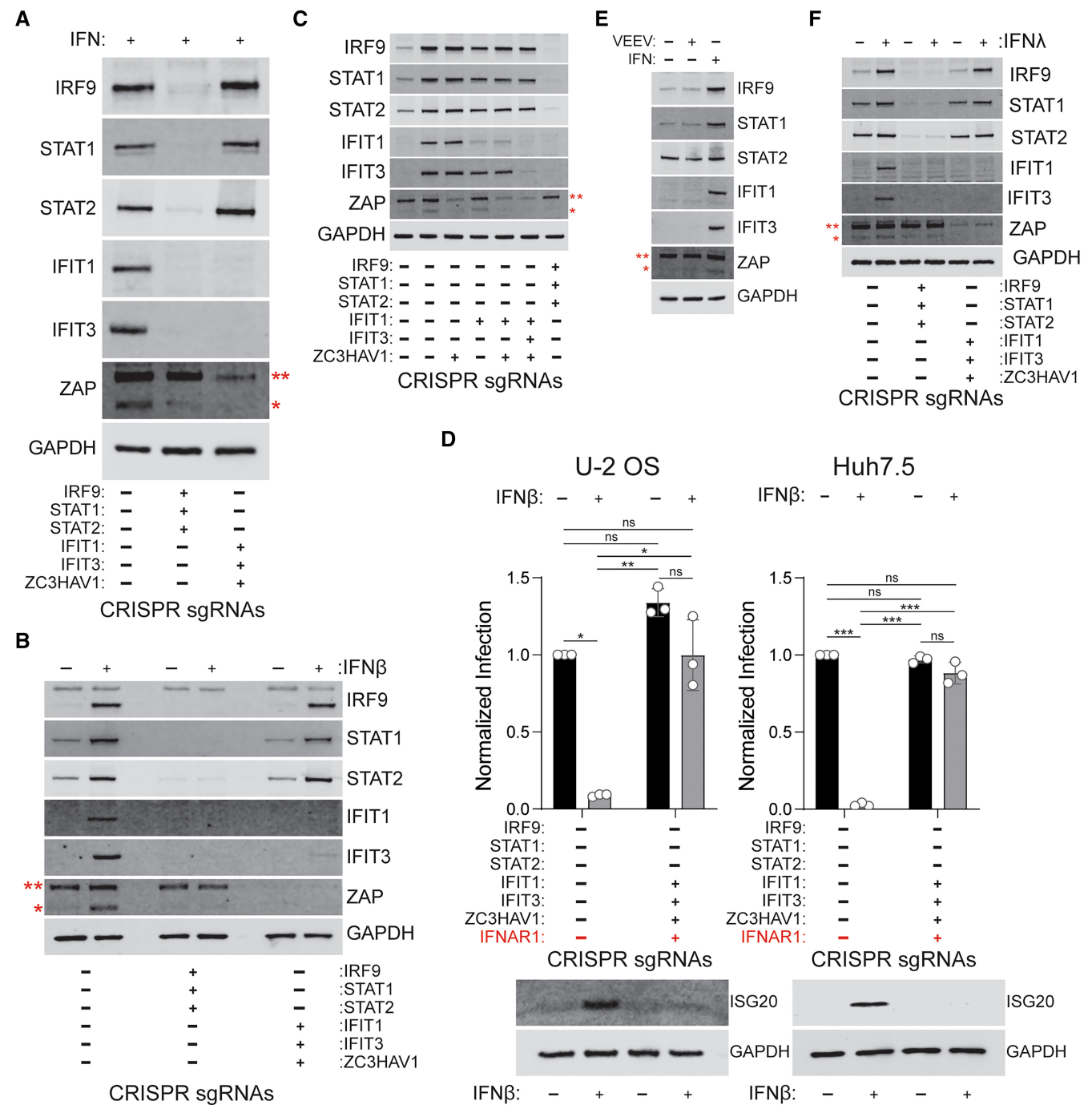


Figure EV1.

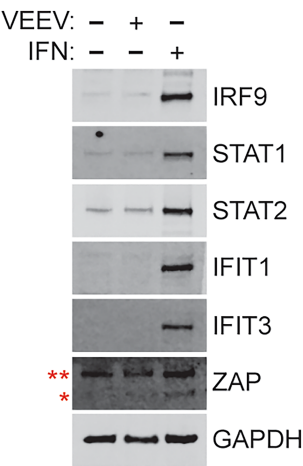


Figure EV2. VEEV infection alone does not induce selected ISGs.

Western blot from lysates of U-2 OS cells after 12 h infection with VEEV TC-83 or IFN β treatment (20 U/ml for 24 h). Red asterisks denote long (**) and short (*) isoforms of ZAP.

Source data are available online for this figure.