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**Supplemental Information**

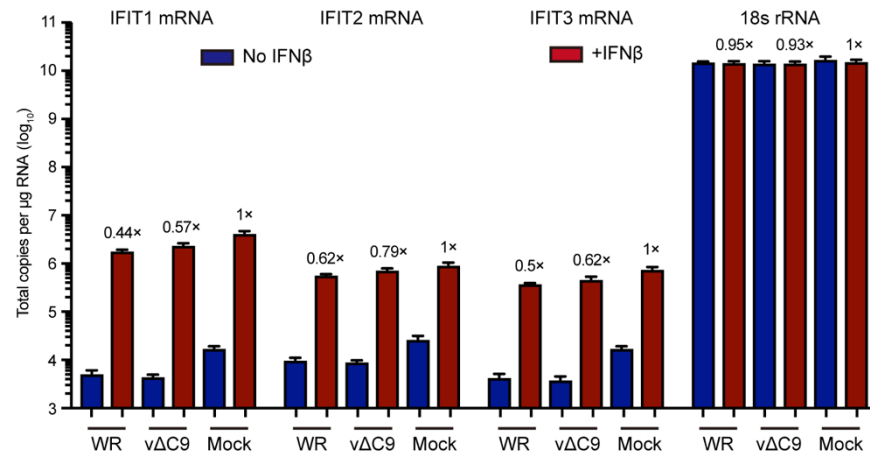
**Vaccinia Virus Ankyrin-Repeat/F-Box**

**Protein Targets Interferon-Induced**

**IFITs for Proteasomal Degradation**

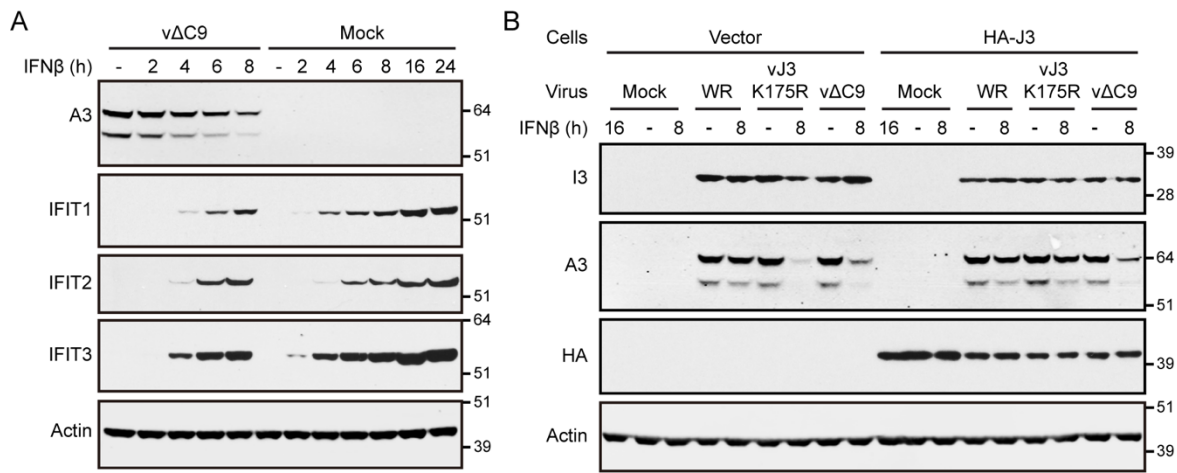
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Figure S1



**Figure S1 (Related to Fig. 4).** Quantification of IFIT mRNAs. A549 cells were mock infected or infected with 3 PFU per cell of VACV WR or v $\Delta$ C9 in triplicate. After 6 h, cells were harvested for RNA extractions, which were performed on separate days for each replicate. Following reverse transcription, the RNAs were quantified by ddPCR. The numbers above the bars indicate the amounts relative to mock. Errors bars are SEM.

Figure S2



**Figure S2 (Related to Fig. 6).** Effect of ectopic expression of HA-J3 MTase on IFN-sensitivity of VACV mutants. **(A)** A549 cells were not treated (-) or treated with IFN $\beta$  for 2 to 8 h and at each time point were infected with v $\Delta$ C9 for 8 additional hours and then harvested. Additional A549 cells were mock-infected and harvested after treatment with IFN $\beta$  for 2, 4, 6, 8, 16 and 24 h. Expression of VACV A3 and cellular IFITs were determined by Western blotting. **(B)** Effects of ectopic HA-J3 expression on IFN-sensitivity of VACV mutants. Untreated (-) or IFN $\beta$ -pretreated (+) A549 cells and A549 cells expressing HA-J3 were mock-infected or infected with VACV WR, vJ3<sub>K175R</sub> or v $\Delta$ C9. At 8 h post-infection the lysates were analyzed by Western blotting. The numbers on the right indicate the mass in kDa and positions of standard markers. In A and B, representatives of two biological repeats are shown.