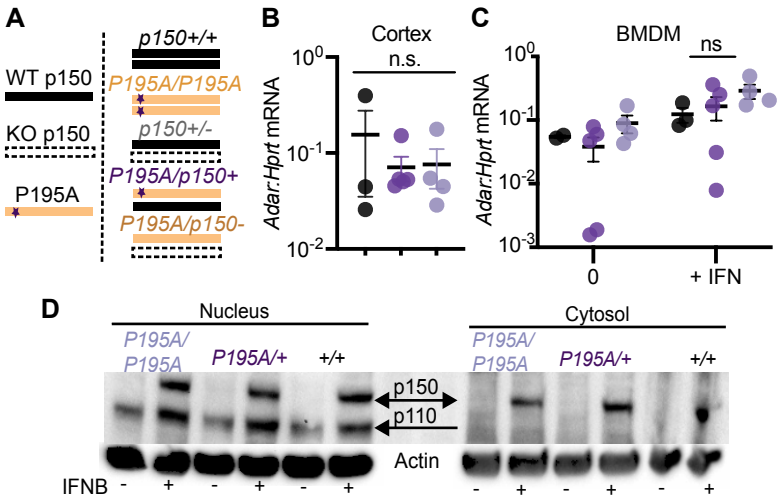


Figure S1, refers to Figure 1: Characterization of the *Adar P195A* mouse model

(A) Schematics representing the different *Adar p150* alleles, and different *Adar*$^{P195A/p150}$ genotypes.

(B) Expression of *Adar* mRNAs in the cortex of *Adar*$^{P195A/P195A}$, *Adar*$^{P195A/+}$ and *Adar*$^{+/+}$ mice.

(C) Expression of *Adar* mRNAs in BMM from *Adar*$^{P195A/P195A}$, *Adar*$^{P195A/+}$ and *Adar*$^{+/+}$ mice, with and without 24 hour treatment with recombinant IFNβ. Bars represent mean and SEM. (D) Western blot for ADAR1 in the cytosol and nucleus of primary MEFs of the indicated genotypes with and without 24 hour treatment with recombinant IFNβ.

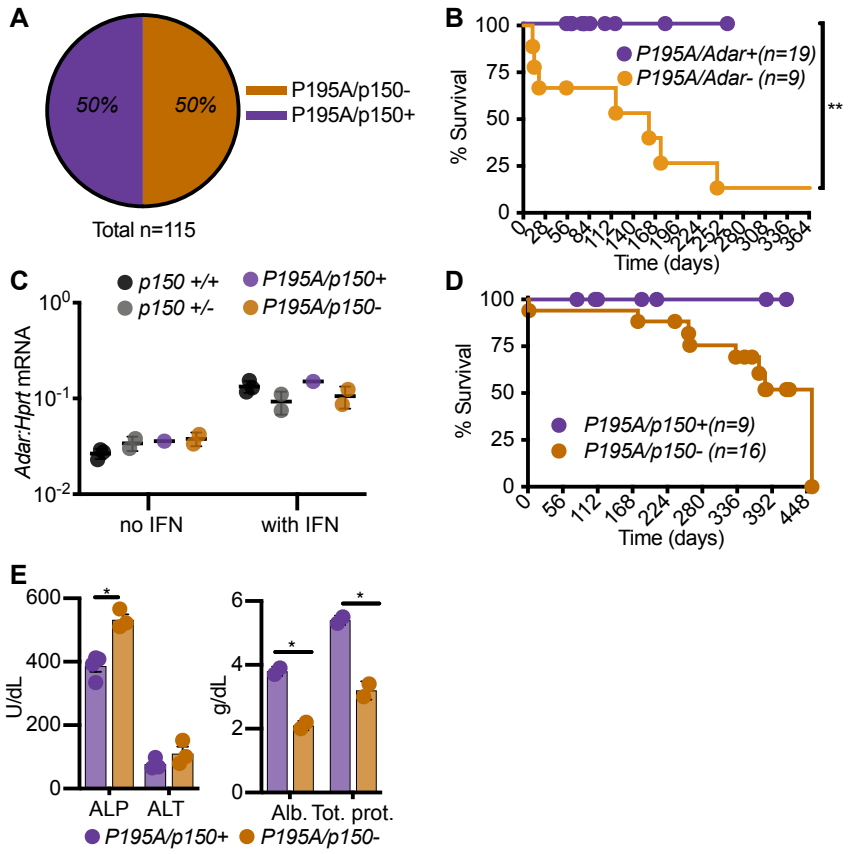


Figure S2, refers to Figure 2: *Adar*^{P195A} mice crossed to *Adar* null alleles exhibit MDA5-dependent pathology

(A) Percentage of mice of the indicated genotype born from crosses of *Adar*$^{P195A/P195A}$ and *Adar*$^{+/-}$ mice (left panel), and *Adar*$^{+/+}$ and *Adar*$^{+/-}$ mice (right panel). Number of each genotype is indicated in parentheses. *Adar*$^{+/-}$ mice are born at a lower than Mendelian frequency, as has been previously observed (Pestal et al., 2015).

(B) Percentage of mice of the indicated genotype born from crosses of *Adar*$^{P195A/P195A}$ and *Adar p150*$^{+/-}$ mice (right panel).

(C) Survival of mice of the indicated *Adar* genotype on an *Ifih1*$^{+/-}$ background, revealing partial rescue from mortality.

(D) Survival of mice of the indicated *Adar p150* genotype on an *Ifih1*$^{+/-}$ background, revealing partial rescue from mortality.

(E) Expression of *Adar* mRNA transcript in independently derived primary MEFs of the indicated genotypes, with and without 24 hours of treatment with recombinant mouse IFNβ. Bars represent mean and SEM.

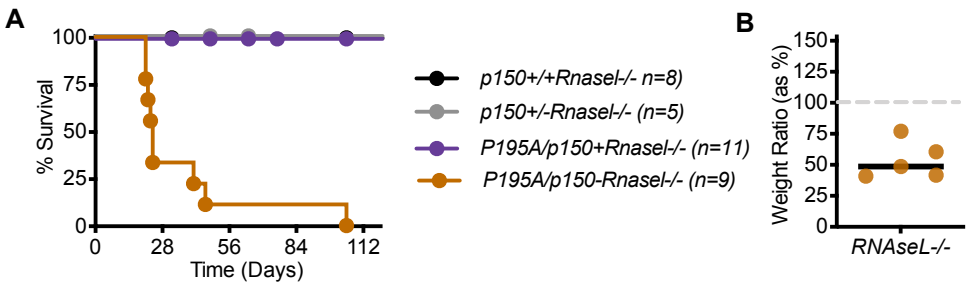


Figure S3, refers to Figure 5: RNase L deficiency does not rescue *Adar*$^{P195A/p150-}$ mice

(A) Survival of *Rnasel*$^{-/-}$ mice of the indicated genotype: *Adar p150*$^{+/+}$ (n=8), *Adar p150*$^{+/-}$ (n=5), *Adar*$^{P195A/p150+}$ (n=11), *Adar*$^{P195A/p150-}$ (n=9).

(B) Weights, measured at 23 days, of *Adar*$^{P195A/p150-}$*Rnasel*$^{-/-}$ mice, as a percentage of the average weight of age- and sex-matched *Adar*$^{P195A/p150+}$*Rnasel*$^{-/-}$ control mice.

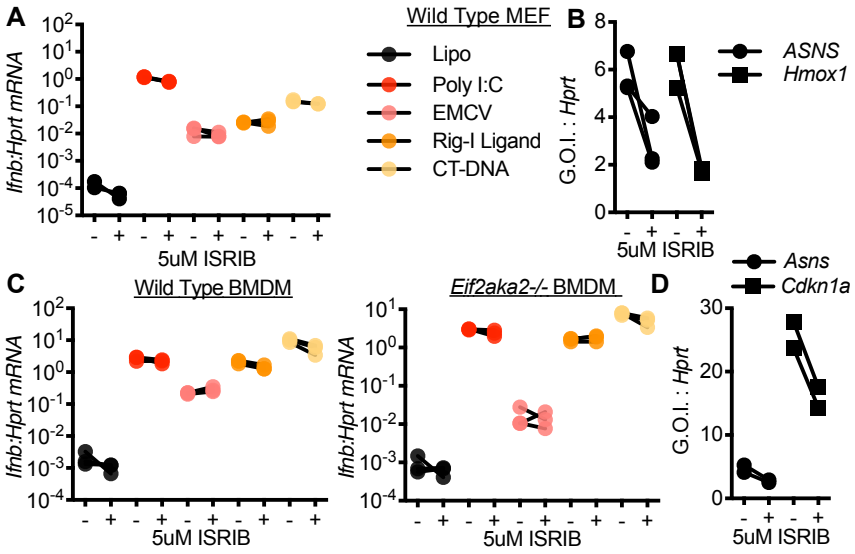


Figure S4, refers to Figure 5: ISR blockade or PKR deficiency does not affect *Ifnb* production

(A) Expression of *Ifnb* mRNA transcript in primary MEFs 6 hours after transfection with the indicated stimulus, or infection with EMCV. n=3 replicates. Data is representative of two independent repeats.

(B) Expression of ISR transcripts in response to 6 hours of thapsigargin treatment, with and without 5μM ISRIB treatment.

(C) Expression of *Ifnb* mRNA transcript in primary WT or *Eif2ak2*$^{-/-}$ BMM 6 hours after transfection with the indicated stimuli, or infection with EMCV.

(D) Expression of ISR transcripts in response to 6 hours of thapsigargin treatment in BMMs, with and without 5μM ISRIB treatment.

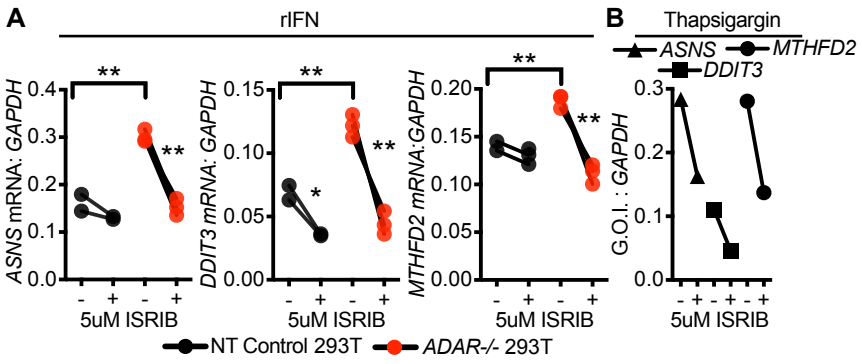
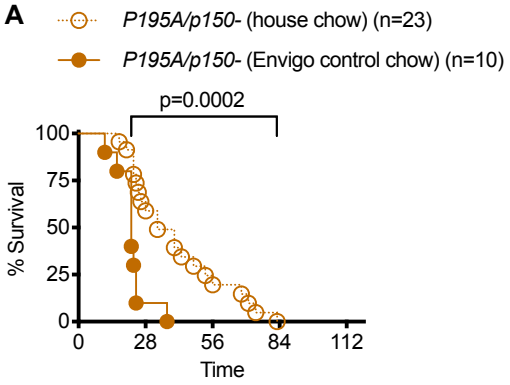


Figure S5, refers to Figure 7: ISR induction in clonal human *ADAR* deficient HEK 293T cells.

(A) Expression of ISR transcripts in non-targeting control or *ADAR*-deficient 293T cells, 72 hours after addition of 1000U rIFNβ. Data is representative of two independent experiments. (B) expression of ISR transcripts in non-targeting control 293T cells after treatment with thapsigargin, with or without ISRIB.

A



B

	BioServ: House Chow	Envigo: 2BAct and 2BAct contol chow
% Fat	14.5	4.0
% Protein	13.6	14.3
% Fiber	9.0	22.1
% Ash	3.0	4.7
% Carb	52.9	48.0
Vit. A IU/G	93.0	6.0
Vit. D IU/g	9.3	0.6
Vit. E IU/kg	13.2	120.0
Vit. K mg/kg	0.0	20.0
Niacin mg/kg	10.8	54.0
Biotin mg/kg	0.0	0.3

Figure S6, refers to Figure 7: Survival of *Adar*$^{P195A/p150-}$ mice on different mouse diets.

(A) Survival of *Adar*$^{P195A/p150-}$ mice on in-house control chow (n=23) and Envigo control chow (n=10).

(B) Comparison of the contents of in-house mouse chow, used for pups in Figures 1-6, and the Envigo control chow, used in Figure 7 to match the nutrient content of the chow into which the 2BAct was formulated.