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SUPPLEMENTARY INFORMATION

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Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade

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Supplementary Text:

I. Enhanced responses to checkpoint blockade in *Adar1* null tumors are not driven by engraftment efficiency or tumor size at the time of treatment

We considered the possibility that improved responses to checkpoint blockade in *Adar1* null tumors were due simply to poor engraftment of *Adar1* null tumor cells, which could make them more responsive to treatment by virtue of smaller tumor size at the outset of therapy. To test this, we enforced equivalent size of tumors at the beginning of PD-1 treatment by increasing the number of inoculated *Adar1* null tumor cells and using Matrigel to enhance engraftment. Despite matched sizes at the start of treatment, *Adar1* null tumors remained significantly more susceptible to immunotherapy compared to similarly sized control tumors (Extended Data Fig. 1e). Thus, a difference in tumor size at the initiation of treatment does not explain the profound sensitivity of *Adar1* null tumors to checkpoint blockade.

II. Hyperediting in human tumors is associated with decreased immune infiltration and inflammatory response

Many human tumors have amplifications of the *ADAR1* locus[40-42] and increased A-to-I editing levels compared to non-malignant tissues[37, 43]. We reasoned that *ADAR1* amplification might prevent immunostimulatory dsRNA from eliciting an inflammatory response. To determine whether increased A-to-I editing of dsRNA in human tumors was associated with reduced inflammation in human cancer, we compared levels of RNA hyperediting previously characterized within The Cancer Genome Atlas (TCGA)[37] to gene expression signatures of inflammatory response and immune infiltration[31, 38]. We found that increased A-to-I hyperediting was negatively correlated with expression signatures of inflammation ($P = 1.98e^{-6}$, Kolmogorov-Smirnov test), response to IFNγ ($P = 0.012$), evidence of apoptosis ($P = 1.113e^{-7}$), as well as two measurements of inferred immune infiltration (Extended Data Fig. 8a and b, $P = 9.108e^{-6}$ and 0.0029). This suggests that RNA editing may play a role in constraining anti-tumor immune responses in human cancer.

Supplementary Information References

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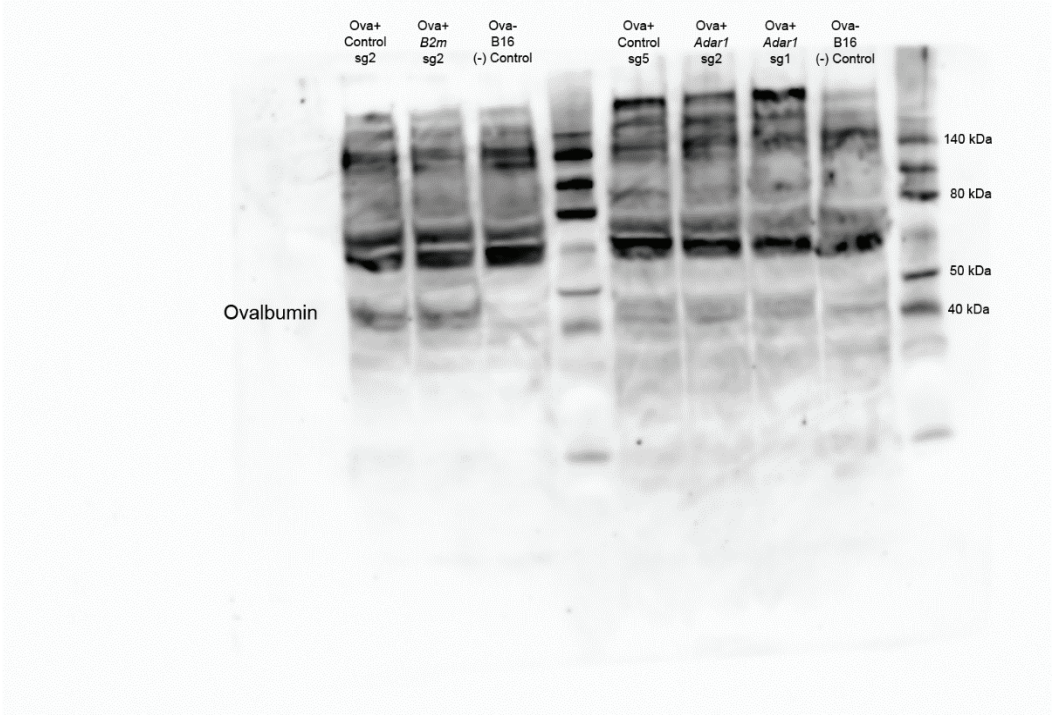
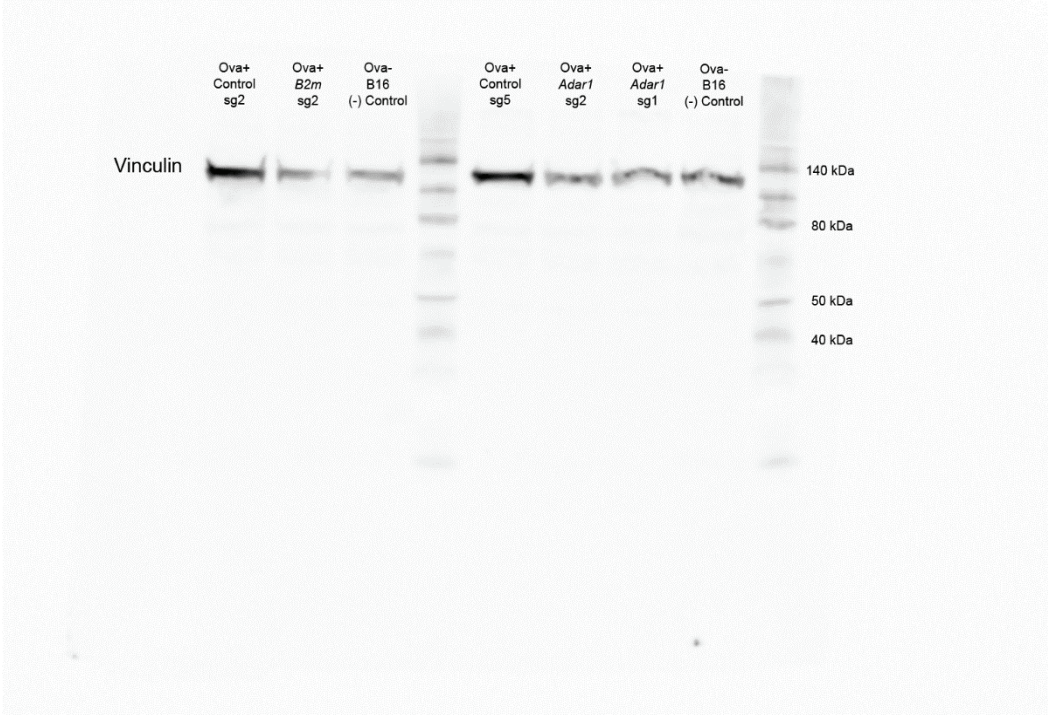
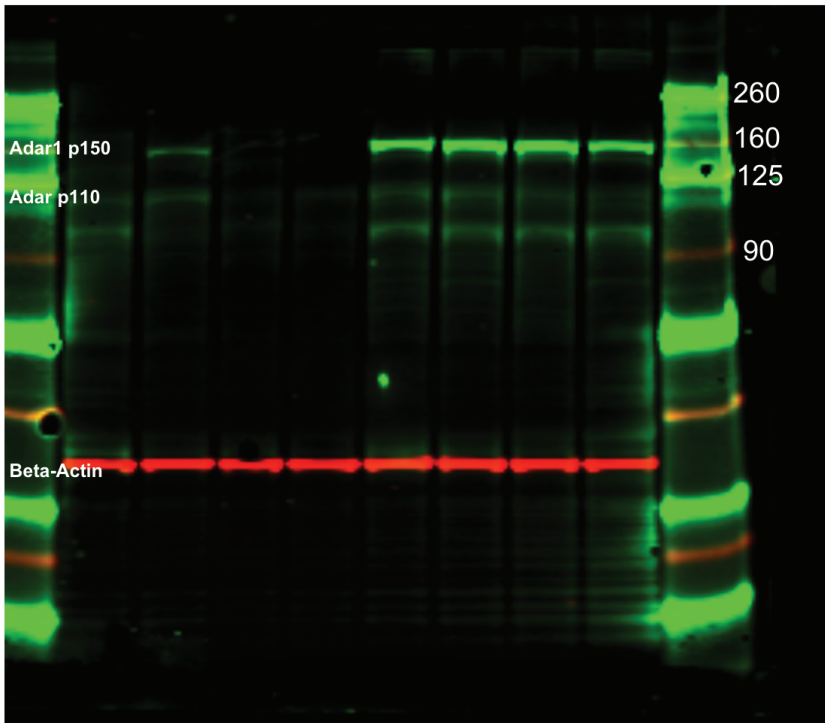
Extended Data Figure 1a

Extended Data Figure 5a

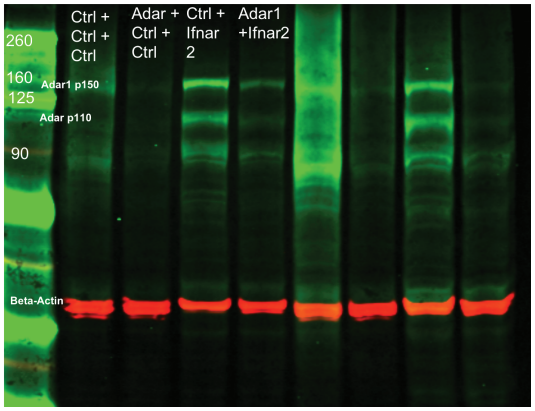


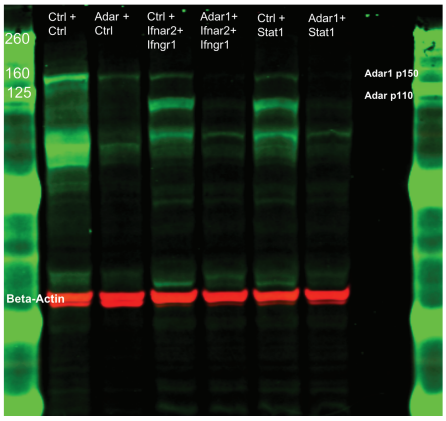


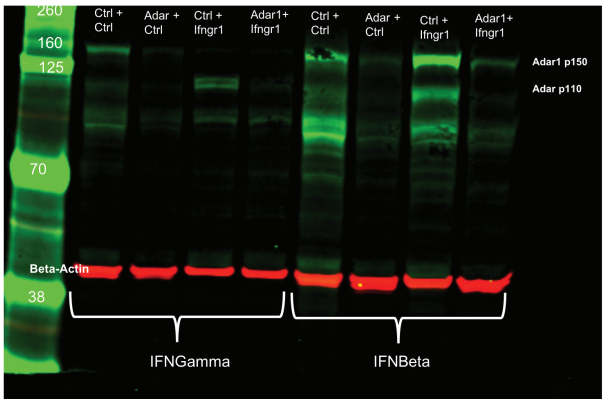
Extended Data Figure 6a

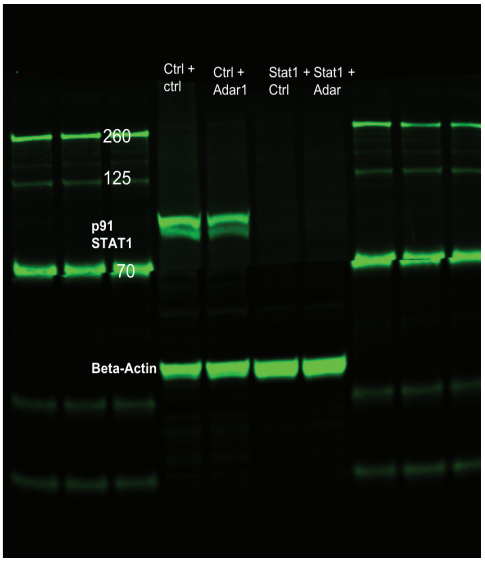


Extended Data Figure 6c

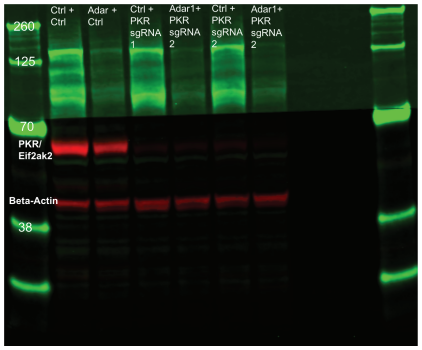


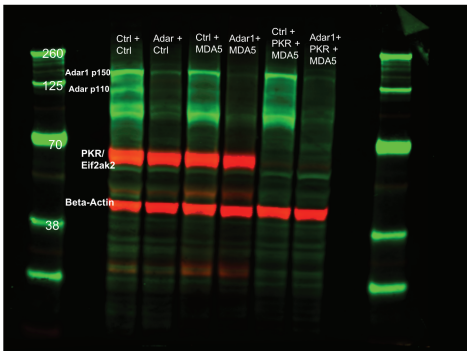


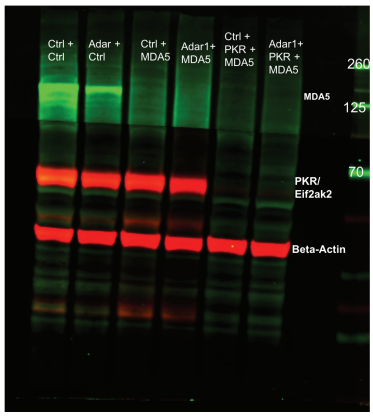


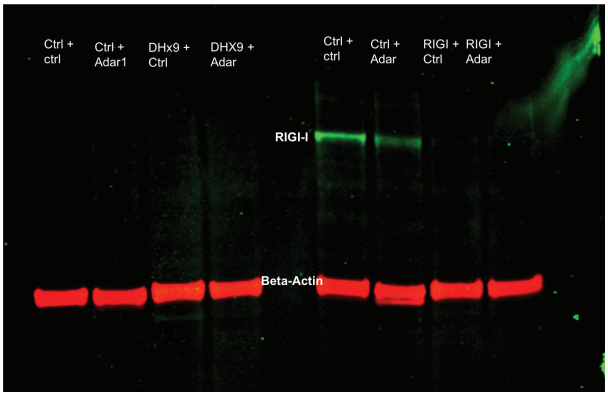


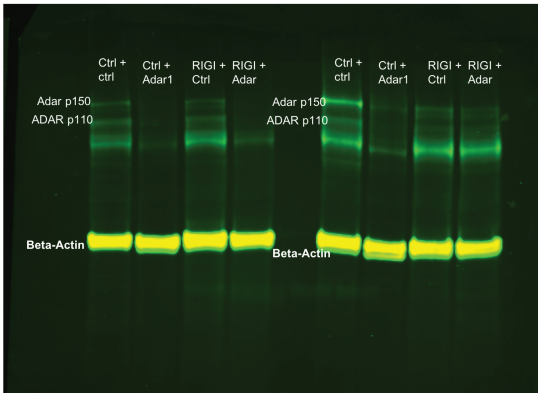
Extended Data Figure 7e

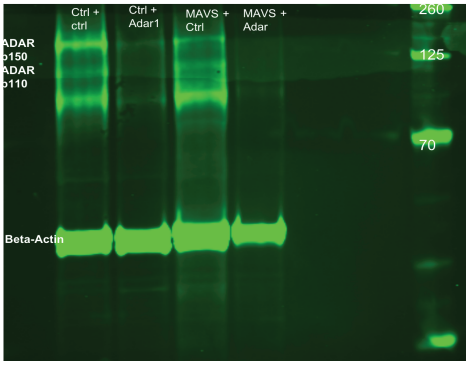




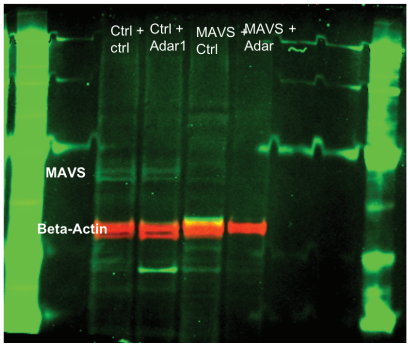


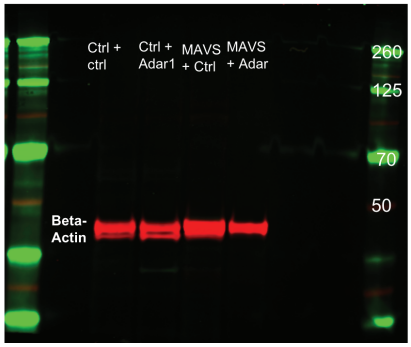






Same Blots, different exposure of the 800nm Green





Extended Data Figure 9a