Adar-mediated RNA editing in pancreatic β-cells prevents aberrant innate immune activation and diabetes

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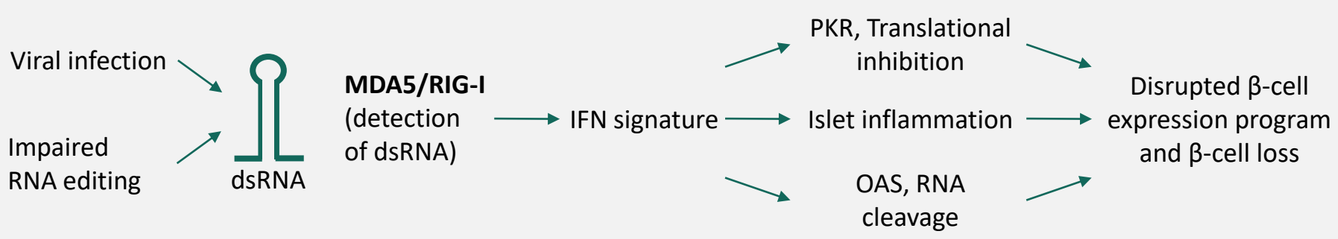
Background

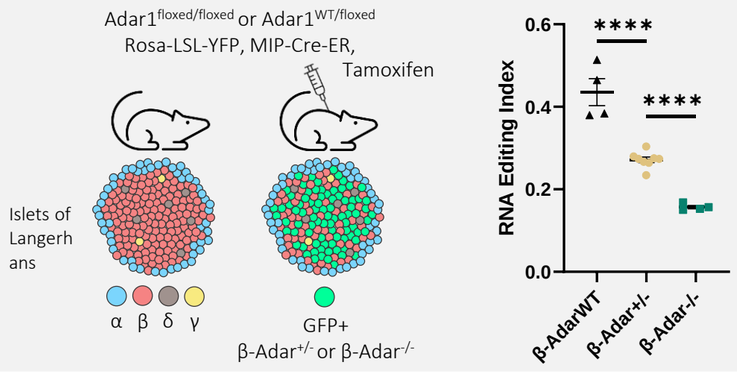
RNA editing is a widespread cellular process involving the deamination of some adenosines to inosines in double-stranded RNA (dsRNA) structures by the ADAR (Adenosine Deaminase Acting on RNA) enzyme family. ADAR1 is the main RNA editor in mammals. The prime ADAR1 substrates are retroelements inserted in inverted orientation in non-coding regions of transcribed genes. Such transcripts form viral-like dsRNA structures that, unless edited by ADAR1, could activate the dsRNA sensor MDA5 to initiate an interferon response. Thus, a vital function of ADAR1 is to disrupt self-dsRNA molecules to prevent inappropriate activation of anti-viral immunity. While RNA editing has been studied in different organs and in cancer, little is known about its role in beta-cell function and health. This is particularly relevant since Type 1 diabetes (T1D) is typically preceded by an IFN-I transcriptional signature. Moreover, T1D genome wide association studies (GWAS) have identified risk and protective variants in the IFIH1 gene that encodes the dsRNA sensor MDA5. Thus, *in-vivo* disruption of Adar in mouse beta-cells might mimic early events preceding autoimmunity, enabling to dissect the mechanisms by which IFN-I signaling and immune cell-beta-cells interplay contribute to beta-cell dysfunction or loss.

1. Model for the possible involvement of impaired RNA editing in autoinflammation-driven diabetes

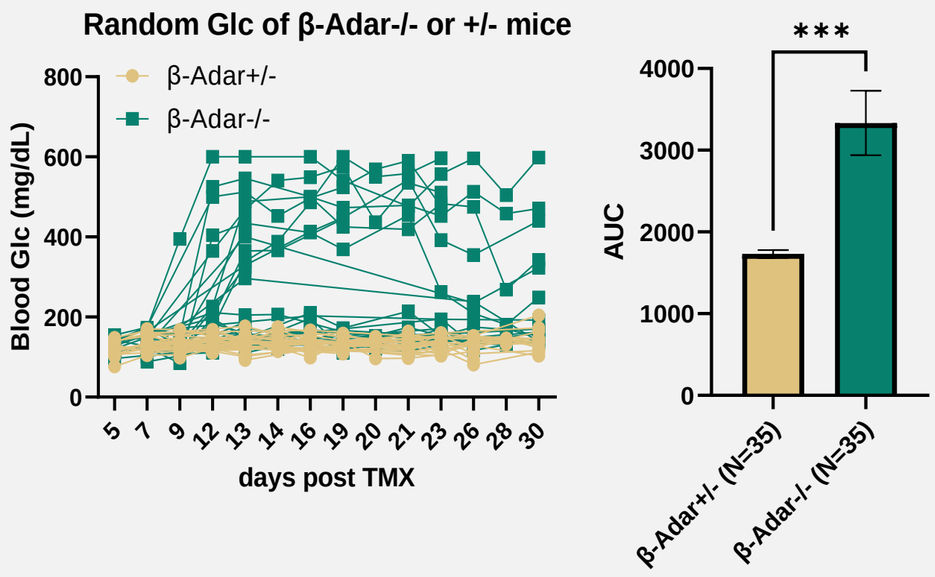


2. Method : mouse models

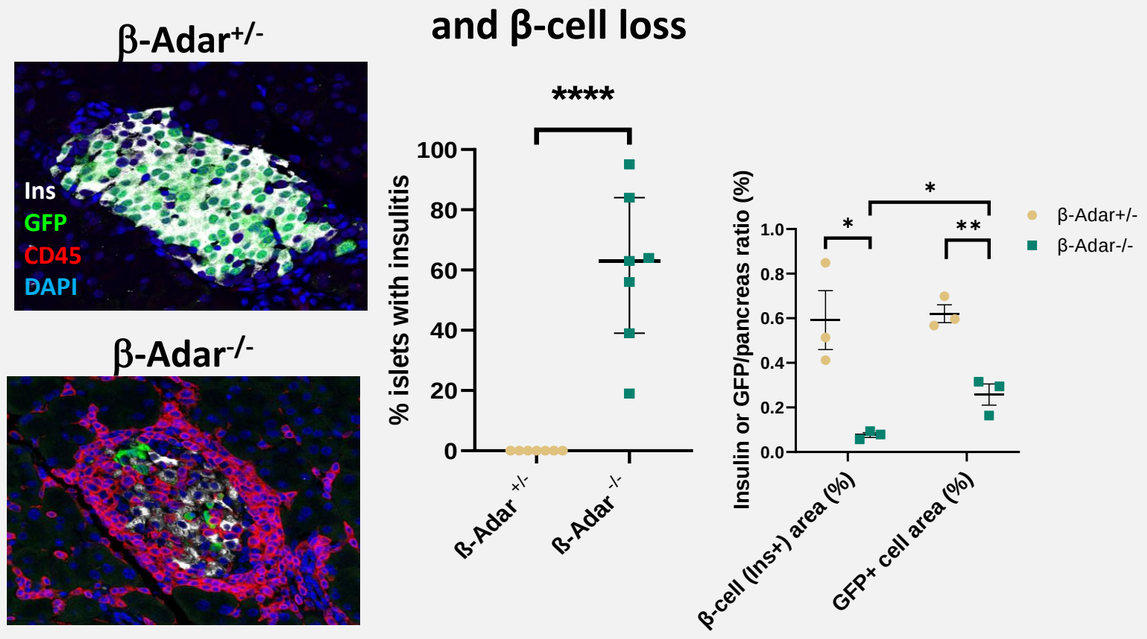
Specific deletion of Adar in β-cells by tamoxifen injection in 1 month-old Insulin-Cre-ERT; Rosa-LSL-YFP mice; Adar F/F or F/+ causes reduced RNA editing in adult β-cells.



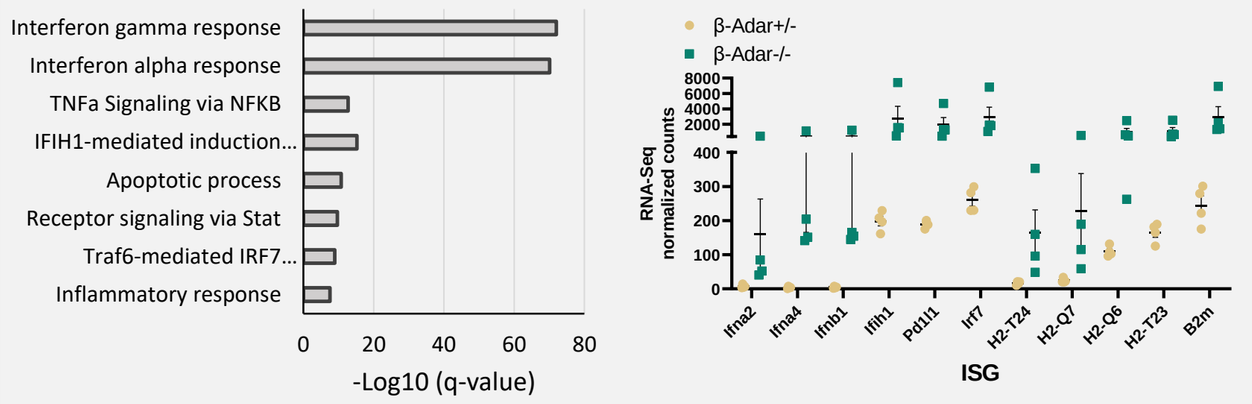
3. β-cell-specific Adar KO causes diabetes



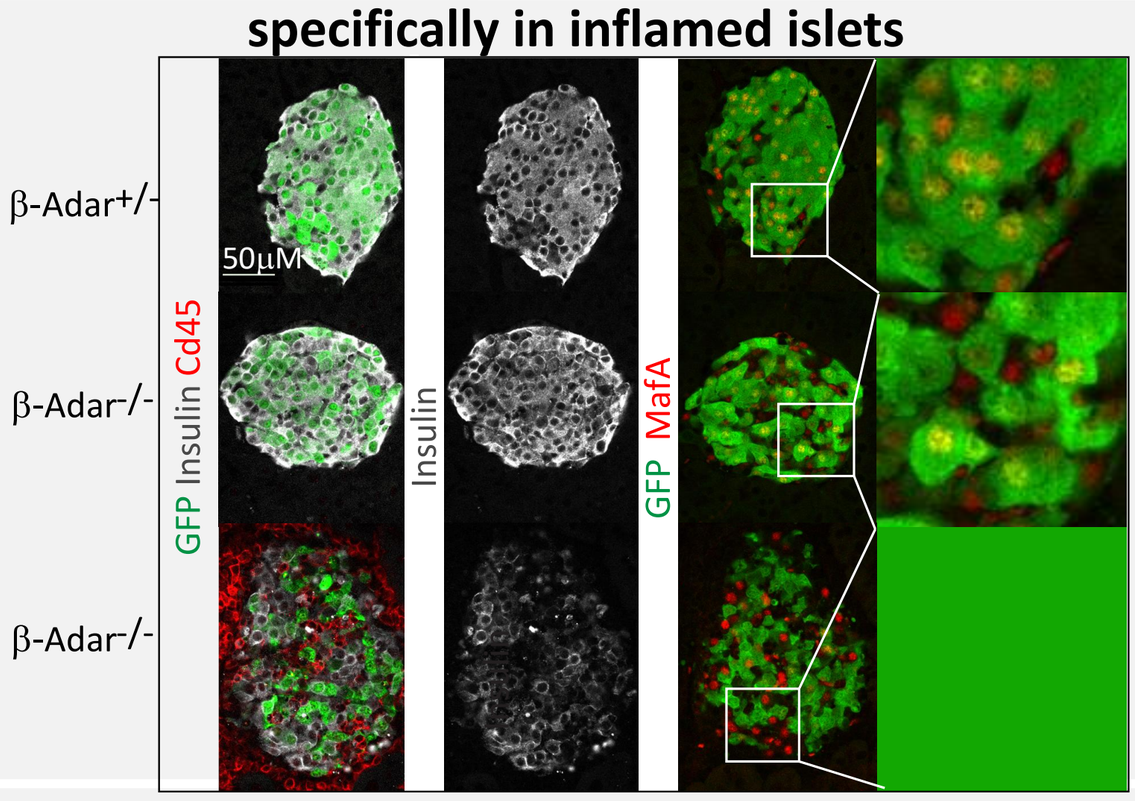
Adar loss in β-cells causes islet autoinflammation and β-cell loss



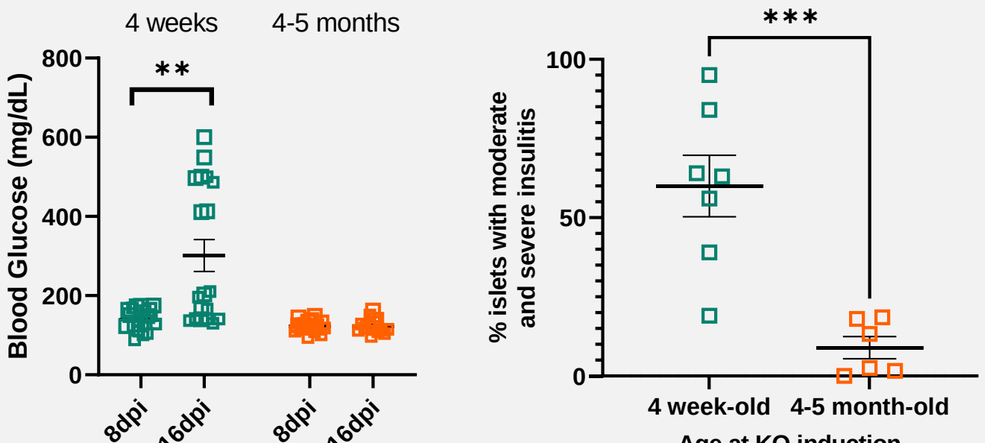
4. ISGs are upregulated in β-Adar$^{-/-}$ cells



5. Adar loss disrupts β-cell expression program, specifically in inflamed islets

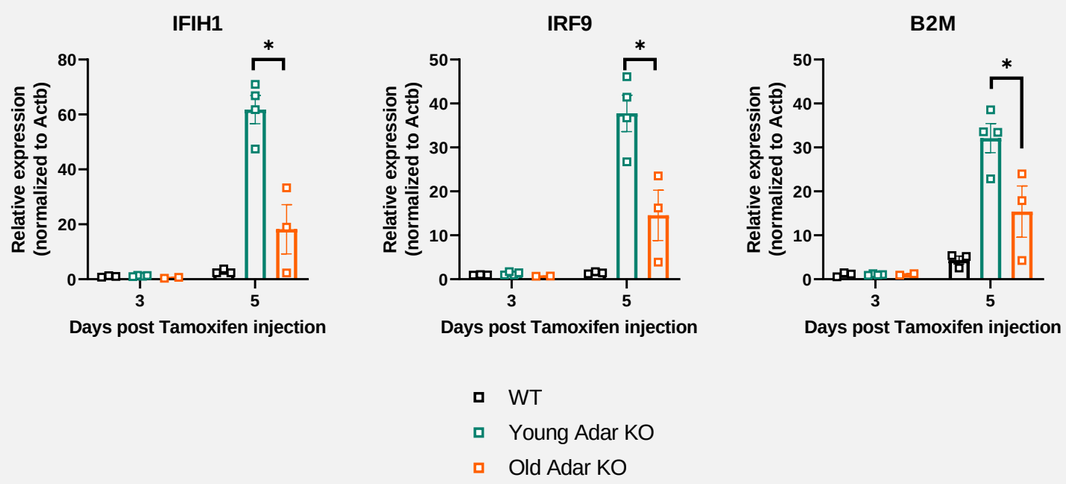


6. Adar loss in 6-month-old mice results in milder inflammation and does not cause diabetes



7. Age attenuates the induction of ISGs in islets from β-Adar-KO mice

Islets were extracted 3 days after Tamoxifen injection from 1- or 6-month-old mice and cultured *ex-vivo* for 48h before RNA extraction.



Conclusions

- Specific disruption of Adar in β-cells from 1-month-old mice causes massive IFN response, islet inflammation, β-cell destruction and diabetes.
- Adar loss impairs β-cell expression program cell autonomously, but these effects depend on paracrine signals produced by inflammatory cells.
- The Insulitis and diabetic phenotype of β-Adar mutant mice, as well as the interferon response initiated by Adar mutation in β-cells are dampened with age.
- Ongoing experiments are aimed at characterizing the involvement of adaptive and innate immune cell subpopulations in the development of diabetes in Adar-mutant mice.