The role of RNA editing in α and β cells

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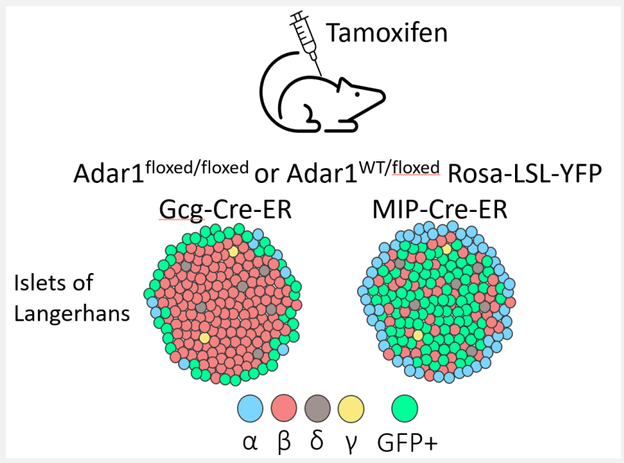
Background

RNA editing, involving adenosine deamination by ADAR1, serves to dismantle endogenous double-stranded RNA (dsRNA) structures that could potentially mimic viral infection and trigger autoinflammation. Despite its emerging central role as a regulator of inflammation, A-to-I RNA editing has not been studied in pancreatic islets.

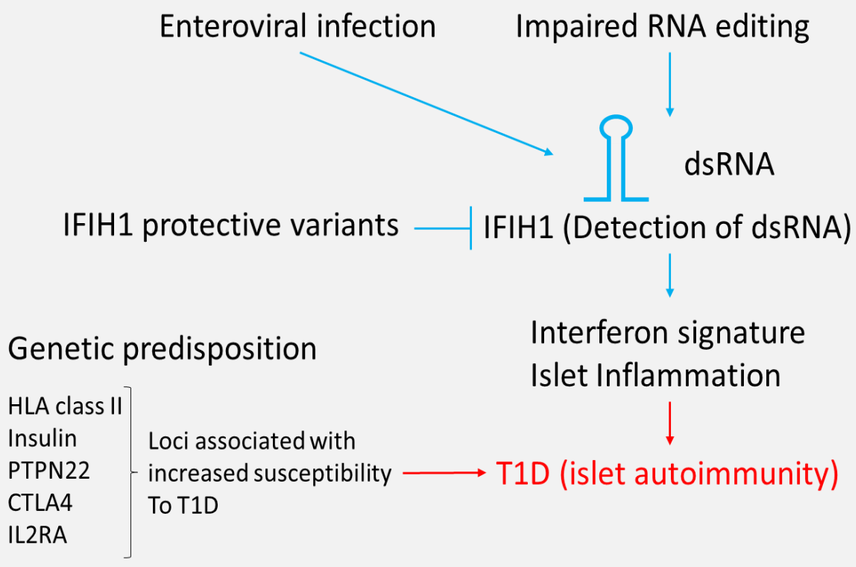
We hypothesize that RNA editing serves to limit autoinflammation in islets, and that its disruption may model early stages of type 1 diabetes, involving an interferon response. To test this hypothesis we characterized the impact of disrupted RNA editing in mouse islets, using tamoxifen-inducible deletion of ADAR1 in β-cells or α-cells in vivo.

1. Method : mouse models



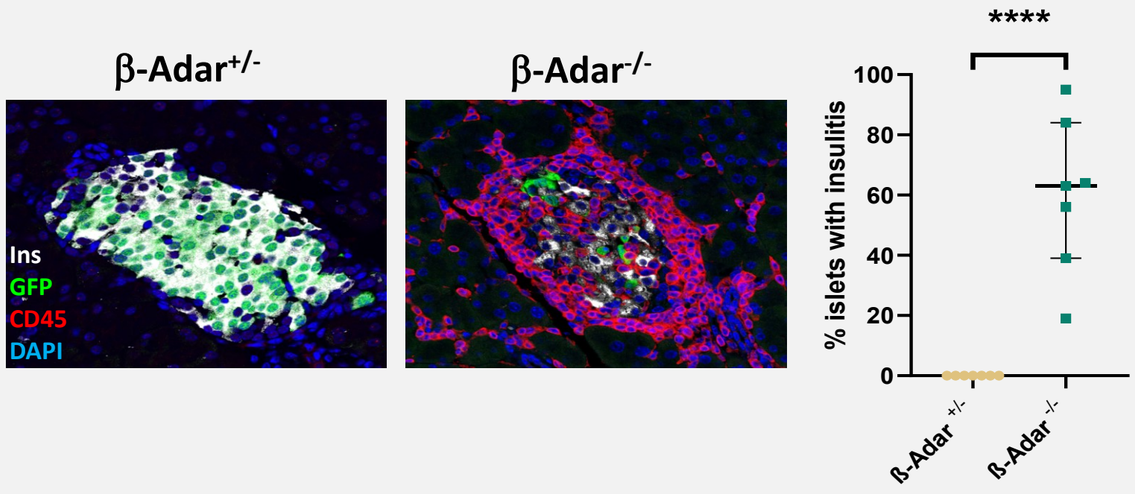
Deletion of ADAR1 in β-cells or α-cells by tamoxifen injection to 1 month-old Insulin-CreERT or Glucagon-CreERT; Adar1 F/F; Rosa-LSL-YFP mice.
This results in disruption of RNA editing in adult β-cells/α-cells.

2. Model for possible involvement of impaired RNA editing in the etiology of T1D

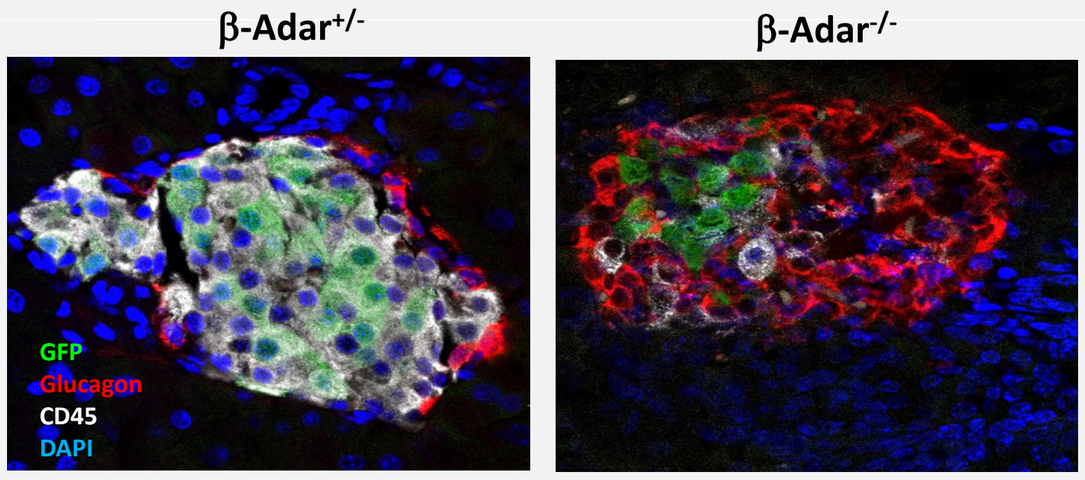


3. Effects of β-cell-specific ADAR1 knockout

Adar1 loss in β-cells causes islet autoinflammation and β-cell loss

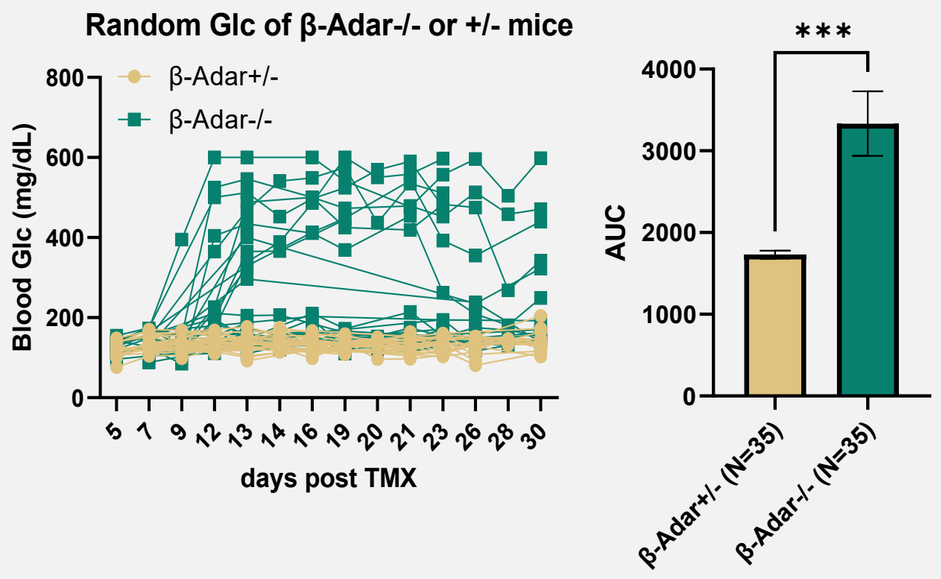


4. Preservation of α-cells in β-cell-specific ADAR1 knockout

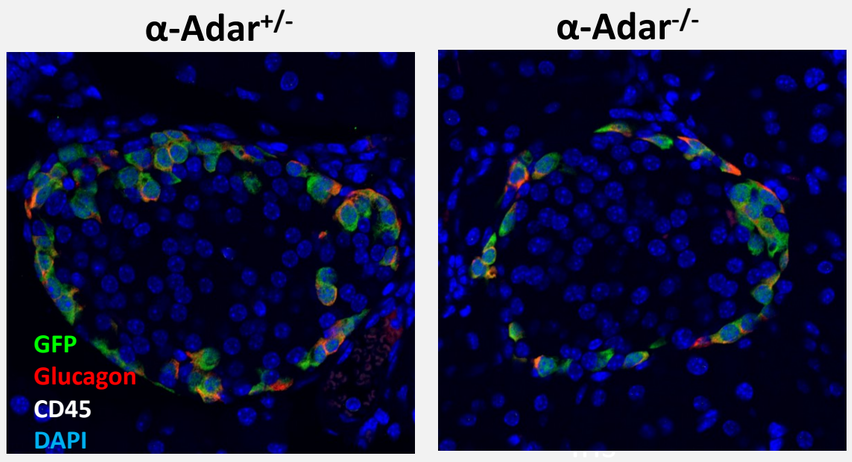


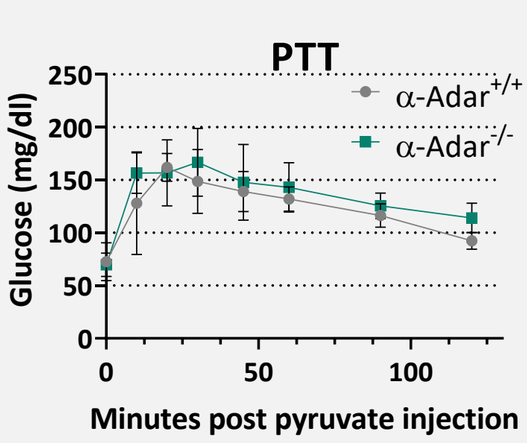
Results so far suggest that α-cell numbers remain unchanged in β-Adar$^{-/-}$ mice, despite massive islet inflammation and beta cell destruction.

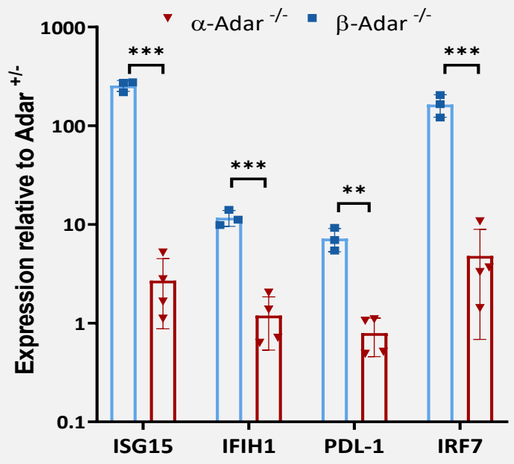
Adar1 loss loss in β-cells causes disruption of glucose homeostasis



5. α-cell-specific ADAR1 knockout does not elicit inflammation and does not impair α-cell function







Weaker interferon response in cultured islets from α-Adar$^{-/-}$ compared to β-Adar$^{-/-}$ whole islets

Conclusions

- Disruption of ADAR1 specifically in β-cells causes massive islet inflammation, β-cell destruction and diabetes.
- Despite extensive immune response in islets, α-cells remain unscathed, reminiscent of α-cell persistence in T1D.
- Neither an immune response nor a metabolic phenotype is observed upon ADAR1 disruption in α-cells of young mice.
- Cultured islets from α-Adar$^{-/-}$ mice elicit a much weaker interferon response compared with islets from β-Adar$^{-/-}$ mice, suggesting an intrinsic resistance of α-cells to disrupted RNA editing.
- Ongoing experiments are aimed at understanding the molecular basis for the unique resistance of α-cells to ADAR1 deficiency.