SUMMARY (Basic Science) 5/2/25 ciT1zen science

Disrupted RNA editing in beta cells mimics early stage type 1 diabetes, or "ADAR Safeguards Against T1D"

ciT1zen science summary

Source: Knebel et al., 2024, Cell Metabolism 36, 48–61 January 2, 2024.
https://doi.org/10.1016/j.cmet.2023.11.011
Authors: Udi Ehud Knebel, Shani Peleg, Chunhua Dai, Roni Cohen-Fultheim, Sara Jonsson, Karin Poznyak, Maya Israeli, Liza Zamashanski, Benjamin Glaser, Erez Y. Levanon, Alvin C. Powers, Agnes Klochendler, Yuval Dor
Correspondence: agnesk@mail.huji.ac.il (A.K.), yuval.dor1@mail.huji.ac.il (Y.D.)
Date: January 2, 2024 (Published)
Summary:
This research article investigates a novel, virus-independent mechanism for the initiation of type 1 diabetes (T1D). The authors demonstrate, using a mouse model and corroborating human islet data, that a disruption in the RNA editing enzyme adenosine deaminases acting on RNA (ADAR) within pancreatic beta cells leads to the accumulation of endogenous double-stranded RNA (dsRNA). This accumulation triggers a robust interferon (IFN) response, resulting in islet inflammation, beta cell dysfunction, destruction, and ultimately, diabetes. The observed phenotypes bear a striking similarity to the early stages of human T1D. Furthermore, the study reveals a crucial link between glucose metabolism (specifically glycolysis via calcium) and the enhancement of the beta cell IFN response, suggesting a potential "vicious cycle" of inflammation and increased beta cell workload in the development of T1D.
Key Themes and Important Ideas/Facts:

1. **Alternative Mechanism for T1D Initiation (Non-Viral dsRNA):** A major hypothesis for T1D posits viral infection as the trigger for a dsRNA-mediated IFN response and inflammation. However, a causal virus remains elusive. This study presents compelling evidence for a **virus-independent mechanism** driven by **endogenous dsRNA** within beta cells.

- **Quote:** "Here, we use a mouse model, corroborated with human islet data, to demonstrate that endogenous dsRNA in beta cells can lead to a diabetogenic immune response, thus identifying a virus-independent mechanism for T1D initiation."

1. **Role of RNA Editing by ADAR1:** Adenosine to inosine (A-to-I) RNA editing, primarily catalyzed by ADAR1, is crucial for modifying dsRNA structures generated by retroelements in the genome. This editing process is a safeguard against the activation of innate immune sensors like MDA5/IFIH1, which recognize dsRNA and trigger an antiviral IFN-I response.

- **Quote:** "Recent studies indicate that a key role of ADAR1 is to edit double-stranded RNA (dsRNA) structures... Such dsRNA structures are powerful and potentially dangerous activators of dsRNA sensors, such as MDA5/IFIH1, which triggers an antiviral type I interferon (IFN-I) response."
- **Quote:** "Thus ADAR1-mediated A-to-I RNA editing destabilizes A-U base pairing in RNA, preventing pathogenic activation of an IFN response triggered by endogenous dsRNA."

1. **Disrupted RNA Editing in Beta Cells Triggers Interferon Response and Inflammation:** The core finding is that interfering with ADAR activity in beta cells directly leads to an IFN response.

- **Quote:** "We found that disruption of the RNA editing enzyme adenosine deaminases acting on RNA (ADAR) in beta cells triggers a massive interferon response, islet inflammation, and beta cell failure and destruction, with features bearing striking similarity to early-stage human T1D."
- **Quote:** "Adar deficiency induced a classic IFN response, with 69% of the 238 genes upregulated (false discovery rate [FDR] < 0.05) known to be regulated by IFN (Interferome database34), including type I IFN genes (Ifna4, Ifnb1), ISGs such as Isg15 and Irf7, dsRNA sen..."

1. **MDA5 (IFIH1) is Essential for the Inflammatory Response:** The study shows that the inflammatory phenotype observed in ADAR-deficient beta cells is dependent on the dsRNA sensor MDA5 (IFIH1).

- **Quote:** "Next, we crossed bAdarKO mice to Ifih1 (MDA5)-deficient background and found that Ifih1 disruption abolished the inflammatory phenotype in bAdarKO mice... This indicates that islet inflammation in bAdarKO mice is driven by MDA5-mediated dsRNA sensing."
- Genetic association studies (GWAS) have previously linked *IFIH1* variants to T1D risk, further supporting its role in sensing dsRNA in the context of T1D.

1. **Beta Cell Dysfunction and Loss:** Disrupted RNA editing leads to impaired beta cell function and eventual destruction. This is evidenced by reduced insulin staining area, decreased pancreatic insulin content, impaired glucose tolerance, and preferential loss of ADAR-deficient beta cells.

- **Quote:** "The insulin-stained area in the pancreas of diabetic mice was greatly reduced (on average, by 87%), as was pancreatic insulin content... suggesting that in mutant mice, beta cells were eliminated."
- **Quote:** "This finding suggests that the destruction of beta cells upon Adar inactivation is not solely dependent on external cues (see below) but also involves cell-autonomous mechanisms."

1. **Mimicry of Early Human T1D Features:** The observed consequences of disrupted beta cell RNA editing in mice closely mirror key characteristics of early human T1D, including islet inflammation (insulitis) with a mixed immune cell infiltrate (macrophages, T cells, some B cells) and an IFN-I transcriptional signature in islets.

- **Quote:** "In mice lacking ADAR in beta cells, islets are targeted by inflammatory cells resembling insulitis in human type 1 diabetes."
- **Quote:** "Overall, the combination of autonomous and non-autonomous phenotypes following ADAR disruption in beta cells bears a striking similarity to phenotypes observed in the pancreas of humans with T1D..."

1. **Glucose Metabolism Enhances the Interferon Response:** A significant finding is the discovery that glucose metabolism influences the beta cell IFN response. High glucose levels, and specifically the rate of glycolysis via a calcium-dependent pathway, enhance the induction of interferon-stimulated genes (ISGs) in ADAR-deficient beta cells.

- **Quote:** "Our discovery that the beta cell IFN response is influenced by glucose metabolism potentially explains the association be...tween metabolism and islet inflammation."
- **Quote:** "Culturing bAdarKO islets in 11 mM glucose led to a dramatic elevation of ISGs compared with a culture in 5 mM..."
- **Quote:** "GKA led to the elevated expression of ISGs, even in the presence of 5 mM glucose... indicating that the rate of glycolysis rather than glucose itself is driving ISG expression in bAdarKO islets."

- This suggests a potential link between increased metabolic workload on beta cells and exacerbation of the inflammatory response.

1. **Impact on Beta Cell Identity and Function Markers:** ADAR deficiency and the subsequent IFN signaling disrupt the expression of key beta cell markers, including MafA and proinsulin, which is also a feature observed in T1D.

- **Quote:** "Adar deficiency disrupts expression of key beta cell markers via IFN signaling."
- **Quote:** "Insets show dramatic reduction in MafA coinciding with reduced proinsulin levels in Adar-deficient (GFP-positive) beta cells of inflamed islets..."

1. **Mosaic Islet Infiltration:** The mouse model exhibits mosaic islet infiltration, where some islets are heavily infiltrated while others are spared. This heterogeneity is also an intriguing and unexplained feature in human T1D.

- **Quote:** "In bAdarKO mice, some islets were heavily infiltrated and some completely spared, despite efficient Adar deletion. Mosaic islet infiltration is an intriguing, unexplained phenomenon in T1D."

Methodology Highlights:

- Generation of a mouse model with beta-cell-specific *Adar* disruption (*Mip*-CreER; *Adar*lox/lox mice).
- Use of a Yellow Fluorescent Protein (YFP) reporter to trace recombined (ADAR-deficient) beta cells.
- Corroboration of findings in human islets using ADAR1 knockdown with shRNA.
- Immunofluorescence staining and analysis of pancreatic sections for insulitis, beta cell markers, and immune cell infiltration.
- RNA sequencing (RNA-seq) to analyze gene expression changes in sorted beta cells and islets.
- RT-qPCR and RT-ddPCR to validate gene expression levels, including IFN and ISGs.
- Metabolic analyses, including blood glucose monitoring and glucose tolerance tests.
- Ex vivo islet culture experiments to study the effects of glucose concentration and pharmacological interventions on ISG expression and insulin secretion.
- Crossing the *bAdarKO* mice with *Ifih1* (MDA5)-deficient mice to assess the role of MDA5 signaling.

Implications and Future Directions:

- This study provides strong evidence for a virus-independent pathway to T1D driven by endogenous dsRNA sensing in beta cells due to compromised RNA editing.
- The link between glucose metabolism and the IFN response in beta cells suggests that targeting metabolic pathways or downstream signaling (like calcium flux) might be therapeutic strategies.
- The findings support the importance of the ADAR-MDA5 axis in T1D pathogenesis and highlight the potential of targeting this pathway.
- The mouse model developed in this study serves as a valuable tool for further dissecting the mechanisms of early T1D and testing potential interventions.
- Understanding the mechanisms behind mosaic islet infiltration in this model may provide insights into the heterogeneous nature of beta cell destruction in human T1D.

In Brief Conclusion:

The study by Knebel et al. reveals that defective RNA editing in beta cells, leading to the accumulation of endogenous dsRNA and activation of the MDA5-dependent interferon response, can trigger islet inflammation and diabetes that closely resembles early human T1D. The finding that glucose metabolism enhances this interferon response highlights a potential feed-forward loop contributing to beta cell demise. This research

provides a compelling, virus-independent model for T1D initiation and opens new avenues for therapeutic investigation targeting RNA editing, endogenous dsRNA sensing, or the metabolic modulation of the beta cell inflammatory response.