Genetic protection from type 1 diabetes resulting from accelerated insulin mRNA decay

https://doi.org/10.1016/j.cell.2025.02.018

This article proposes a **new mechanism for genetic protection against type 1 diabetes (T1D)** that centers on the **accelerated decay of insulin mRNA** carrying a protective single nucleotide polymorphism (SNP). The researchers discovered that this protective SNP, **rs3842752 (G>A)**, located in the 3' untranslated region (UTR) of the insulin gene (INS), creates a motif in the insulin mRNA that is recognized and cleaved by the **inositol-requiring enzyme 1a (IRE1a)** during endoplasmic reticulum (ER) stress.

Here's a summary of the key findings and arguments presented in the article:

- **Protective insulin mRNA is a target for IRE1a-mediated decay (RIDD)**. The study found that the protective insulin mRNA variant (INSP) contains a CUGCAG motif and can form a hairpin structure, both required for IRE1a cleavage, unlike the susceptible variant (INSS). In vitro experiments showed that insulin mRNA from individuals with INSP was cleaved faster and more often by IRE1a compared to mRNA from INSS individuals.
- **INSP mRNA is less stable during ER stress in an IRE1a-dependent manner**. Using a dual luciferase reporter assay, the researchers demonstrated that the protective INS 3' UTR led to a significantly larger decline in Renilla luciferase activity during ER stress compared to the susceptible UTR. This breakdown was prevented by an IRE1a inhibitor.
- **Insulin mRNA levels correlate inversely with beta-cell stress only in individuals with INSP**. Single-cell RNA sequencing of human pancreatic islets revealed that as beta-cell stress increased, insulin mRNA levels decreased in donors carrying INSP, but not in those with only INSS. This suggests that the protective SNP enables the breakdown of insulin mRNA during stress. Notably, there was no difference in nascent insulin RNA counts between the variants, indicating no difference in transcriptional activity.
- **Human islets with INSP show improved vitality and function**. These islets exhibited a significantly higher glucose-stimulated oxygen consumption rate (OCR) and secreted more insulin under both low and high glucose conditions compared to islets with only INSS.
- **Islets with INSP accelerate diabetes reversal in mice**. When transplanted into diabetic NOD-SCID mice, islets carrying INSP led to normoglycemia twice as fast as islets with only INSS.
- **INSP is associated with lower neoantigen (INS-DRiP) production and ER stress**. Surrogate beta cells carrying INSP expressed significantly lower levels of the stress-induced neoantigen INS-DRiP during ER stress compared to those with INSS, and this difference was mediated by IRE1a. Additionally, these cells showed lower levels of the ER stress marker XBP1s.
- **Lower levels of TGM2 expression in beta cells with INSP may reduce immunogenicity**. The study found that beta cells carrying INSP expressed lower levels

of TGM2, an enzyme involved in post-translational modification of autoantigens, suggesting reduced immunogenicity.

- **This protective mechanism may act in concert with or instead of the previously proposed central tolerance mechanism**. The earlier hypothesis suggested that the VNTR in the INS promoter protects against T1D by increasing thymic expression of proinsulin. However, this study found no difference in nascent insulin RNA expression in pancreatic beta cells with different INS variants. The authors propose that the peripheral tolerance mechanism mediated by IRE1a-dependent mRNA decay provides an alternative or complementary explanation for genetic protection.
- **The findings highlight the beta cell's active role in the disease process of T1D**. By modulating its own insulin mRNA levels in response to stress based on its genetic makeup, the beta cell influences its immunogenicity and survival.
- **Clinical implications include using INS 30 UTR genotyping to predict islet function for transplantation and as a prognostic biomarker for T1D**. Furthermore, gene editing to introduce the protective SNP in stem-cell-derived beta cells could enhance their resilience and reduce autoimmunity.

In conclusion, this research identifies a novel mechanism of genetic protection in T1D where a specific SNP in the insulin mRNA leads to its accelerated decay by IRE1a during ER stress. This process alleviates stress, reduces the formation of neoantigens, improves beta-cell function and vitality, and ultimately lowers the risk of developing T1D. This discovery emphasizes the critical role of the beta cell in its own fate and suggests new avenues for therapeutic interventions.