Background and aims: Type 1 diabetes (T1D) as well as T1D-associated auto-antibody positivity (AAb^+) has been linked to repeated enteroviral infections during childhood, particularly caused by coxsackieviruses B (CVBs). CVB RNAs have been found in both the exocrine and endocrine pancreas of individuals with T1D and at-risk AAb^+ organ donors. The mechanisms contributing to such enteroviral disposition remain unclear. Here we show that the virus modulates the Hippo pathway and its terminal effector, Yes-associated Protein (YAP), thereby enhancing an antiviral, proinflammatory response in exocrine and endocrine cells of the pancreas.
Materials and methods: Exocrine and endocrine pancreatic cells from organ donors were exposed to CVB4, and the YAP target genes and innate immunity and anti-viral responses analyzed by RT-PCR. Immunohistochemistry (IHC; in paraffin-embedded pancreatic tissue from organ donors with T1D (n=15), AAb^+ (n=15) and age and BMI-matched non-diabetic controls (n=13)) and RNA Scope for YAP was performed and analyzed from the well-characterized cohort of organ donors from nPOD (Network for Pancreatic Organ Donors with Diabetes).
Results: Enteroviral infection in human endocrine islets and exocrine cells led to a 2.4-fold increase in the expression of YAP compared to control ($p<0.05$), together with elevated expression of its classical target genes CTGF, AMOLT2, ANKRD1 as well as STK4 (the gene encoding for MST1). CVB4 infection triggered a robust innate immunity and antiviral response, evidenced by increased CXCL10, OAS1 and IFNβ expression, which was further potentiated by YAP overexpression. The viral capsid-function inhibitor drug pleconaril effectively blocked viral replication and YAP-induced inflammation in human islets during CVB infection, suggesting that viral amplification is a key driver of YAP-induced inflammation. To elucidate these mechanisms in T1D, we analyzed YAP protein and mRNA expression in pancreases from organ donors. We found significantly higher YAP expression in the exocrine pancreas of AAb^+ and T1D donors, compared to nondiabetic individuals (1.2- and 1.7-fold increase in protein in AAb^+ and T1D; 1.3- and 2.2-fold increase in mRNA in AAb^+ and T1D, respectively; $p<0.05$). Enteroviral RNA was predominantly observed in cells expressing YAP. While ductal and centro-acinar cells exhibited the highest levels of YAP in the exocrine pancreas, there was a notable increase in YAP-positive area in endocrine regions in AAb^+ (2.8-fold increase) and T1D donors (4.7-fold increase; $p<0.05$), compared to nondiabetic controls, where YAP was not previously detected. Physiologically, YAP expression is disallowed in mature beta-cells. Importantly, exocrine YAP levels highly correlated with endocrine YAP expression in T1D ($r=0.6964$; $p=0.005$) donors, while there was a similar trend in AAb^+ ($r=0.6242$; $p=0.060$). These data indicate an association of YAP upregulation with T1D; not only in islets but also in the exocrine pancreas.
Conclusion: Our work uncovers YAP hyperexpression in the exocrine pancreas as an early driver of autoimmunity and T1D by potentiating inflammatory signals, leading to immune cell attack and damage to beta-cells. This finding supports the concept of pro-inflammatory bystander activation in the human pancreas.
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Genetic underpinnings of pediatric onset type 1 diabetes in the Canary Islands

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Background and aims: Type 1 Diabetes Mellitus (T1D) is an autoimmune condition whose onset is significantly influenced by genetics, particularly by the human leukocyte antigen (HLA) region on chromosome 6, which contributes to 40-50% of the genetic risk. In addition to the HLA region, researchers have identified over 50 other loci that increase the susceptibility to T1D, with many involved in key functions of the immune system and insulin production. Despite the global prevalence, the Canary Islands exhibit an unexpectedly high rate of T1D, with incidences surpassing the national average in Spain and being among the highest recorded in Europe. Our study aimed to unravel the genetic foundations of this heightened incidence through a comprehensive association study in a well-defined Canarian cohort using different approaches.
Materials and methods: We examined 1,503 individuals, including 480 cases of pediatric onset T1D. We collect demographic and clinical data. Participants provided informed consent for the participation in the study and the use of their biological samples for genetic research. We conduct a genome-wide analysis of over 8 million variants using the Axiom CEU 1 Array (Affymetrix). Local ancestry estimates were obtained for positions shared with reference data from Europe, North Africa, and Sub-Saharan Africa. Deviations in local ancestry between cases and controls were assessed for each ancestry using logistic regressions adjusted for principal components. Quality control procedures for genotyping data and the association study were meticulously executed using R version 3.2.2 and PLINK version 1.07.
Results: Association study results revealed two statistically significant regions correlating with an increased predisposition to T1D, independent of age, sex, or other genetic variations. SNP rs10114525 on chromosome 9 with a p-value of 6.31E-10, and SNPs rs4295687 and rs10550502 on chromosome 8 with p-values of 1.11E-08 and 3.33E-07 respectively, are among the most compelling associations identified. Additionally, chromosome 11 holds significant SNPs such as rs689 and rs3842753, with p-values within the 4.65E-07 to 5.21E-07 range. Currently, an admixture mapping study is underway to evaluate ancestry and genetic mixing in relation to the prevalence of the disease.
Conclusion: Our study sheds light on the genetic underpinnings of pediatric Type 1 Diabetes Mellitus in the Canary Islands and suggests potential avenues for enhanced preventive and diagnostic measures. By uncovering specific genetic markers, we offer a better understanding of the disease's prevalence in the region, which could inform innovative approaches to managing and potentially reducing the incidence of T1D in this distinct population.
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The TEAD activator TT-10 promotes human beta cell regeneration and protects from diabetes induction

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Background and aims: Pancreatic beta-cell regenerative therapy is crucial to restore highly functional beta-cells in both type 1 and type 2