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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	SpectroFlo®, NIS-Elements
Data analysis	Monocle3, MERLIN, flowJO, prism

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The scRNA-seq data that support the findings of this study have been deposited in the Gene Expression Ominibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) under accession code GSE271480 (Xbp1) and GSE144471 (Ire1α). Source data are provided with this paper. All scripts for the integration, network inference and evaluation are available on GitHub.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N.A
Reporting on race, ethnicity, or other socially relevant groupings	N.A
Population characteristics	N.A
Recruitment	N.A
Ethics oversight	N.A

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A minimum of n = 3 or more biological replicates were used for all statistical analyses. Sample sizes were based on pilot experiments and previously published work.
Data exclusions	No data were excluded
Replication	For all experiments, biological replicates are taken into consideration as described in the text
Randomization	Mice from with the same genotype are randomly allocated to different experiments to minimize bias.
Blinding	For ELISA and quantification of IF images and insulitis scoring, each sample was blinded for data analysis to prevent bias.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	anti-Insulin (Linco, 4011-01; 1:200, and Agilent, IR002; 1:6), anti-Glucagon (Cell Signaling, 2760S; 1:100), anti-Somatostatin (Santa Cruz, sc-74556; 1:50), anti-Ki67 (Cell Signaling, 9129; 1:100), anti-CD3 (Novus Biologicals, NB600-1441; 1:100), anti-CD4 (Cell Signaling, 25229; 1:20), anti-CD8 (Cell Signaling, 98941; 1:150), anti-B220 (eBioscience, 14-0452-85; 1:200), anti-XBP1 (Santa Cruz,

	sc-7160; 1:20 and homemade; 1:20), Alexa Fluor 488 (Invitrogen, A-11073; 1:400), and Alexa Fluor 568 (Invitrogen, A-11036; 1:400), anti-CD45 (30-F11), -CD19 (1D3/CD19), -CD3 (145-2C11), -CD4 (17A2), -CD8 (53-6.7), -CD25 (PC61), CD11b (M1/70), -CD11c (N418), and -F4/80 (BM8) (all from BioLegend; 1:100). Intracellular Foxp3 (Biolegend, 150D; 1:20) .
Validation	See validation on the corresponding company website.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Mus musculus, NOD/ShiLtJ, from 3-week-old to 50-week-old
Wild animals	The study did not involve wild animals
Reporting on sex	As the diabetes incidence is significantly higher in female NOD mice, we used only female mice in this study.
Field-collected samples	The study did not involve samples collected from the fields.
Ethics oversight	The animal care and experimental procedures of this study were carried out in accordance with the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The protocol (#M005064-R01-A03 by F.E. for mice) was approved by the University of Wisconsin-Madison Institutional Animal Care and Use Committee.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	N.A.
Novel plant genotypes	N.A.
Authentication	N.A.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Prior to organ dissection, mice were perfused with 20mL PBS to eliminate contaminating blood leukocytes. Single-cell suspensions of the pancreata were prepared by Collagenase P (Sigma-Aldrich) digestion. Cells from pancreatic lymph nodes and spleen were prepared by physical dissociation. All stainings began with incubation with TruStain fcX anti-mouse CD16/32 (BioLegend), followed by cell surface stainings and then intracellular stainings according to eBioscience's protocol.
Instrument	Cytek Aurora Spectral Cytometer
Software	SpectroFlo®, FlowJo software (Tree Star, Inc.).
Cell population abundance	We gated for CD45 and live cell to sort live immune cells.
Gating strategy	1. use FSC-A/SSC-A to gate for cells; 2. use FSCA/FSCH and SSCA/SSCH to gate for single cell; 3. gate for cell types of interests based on single color staining and FMOs

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.