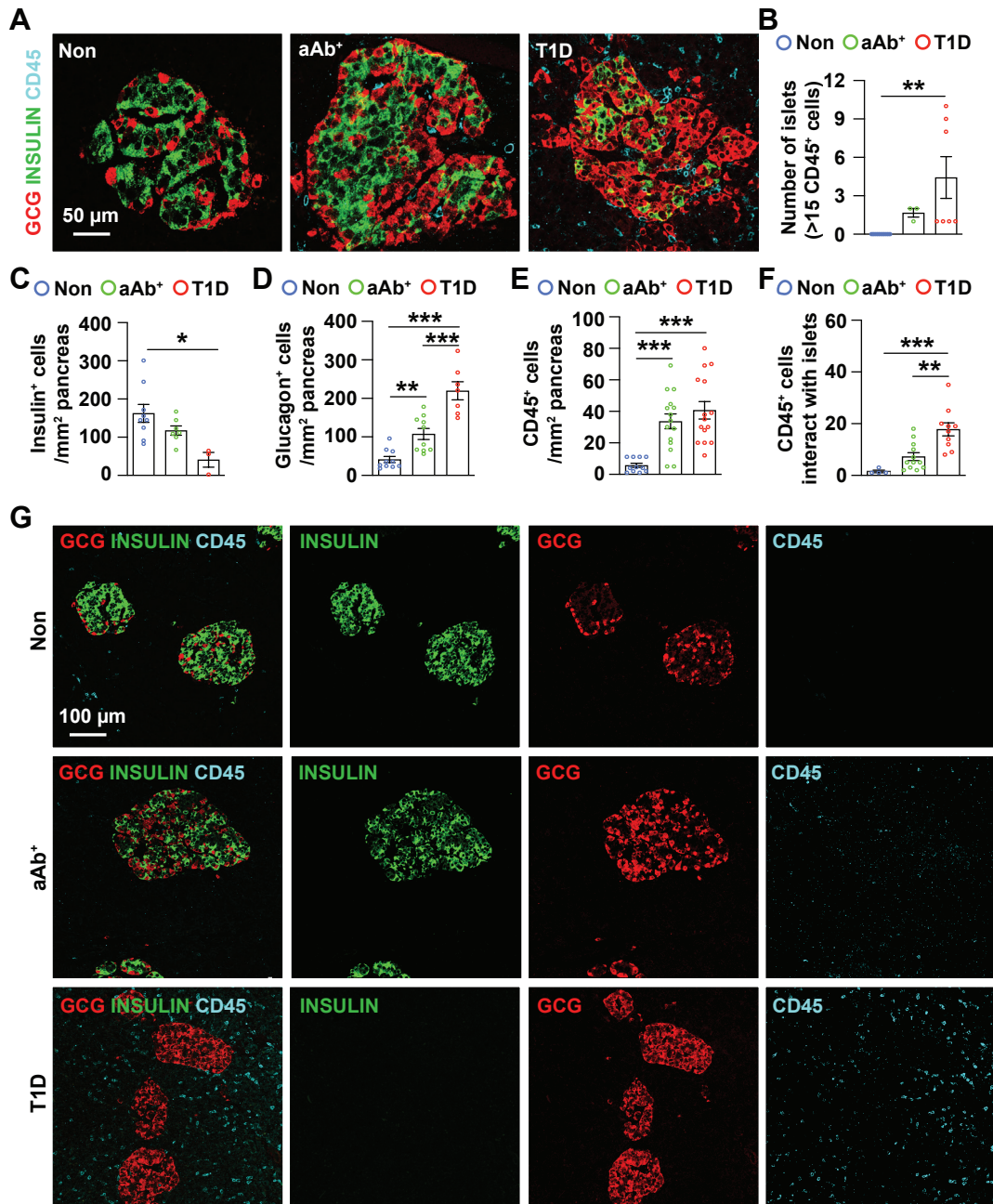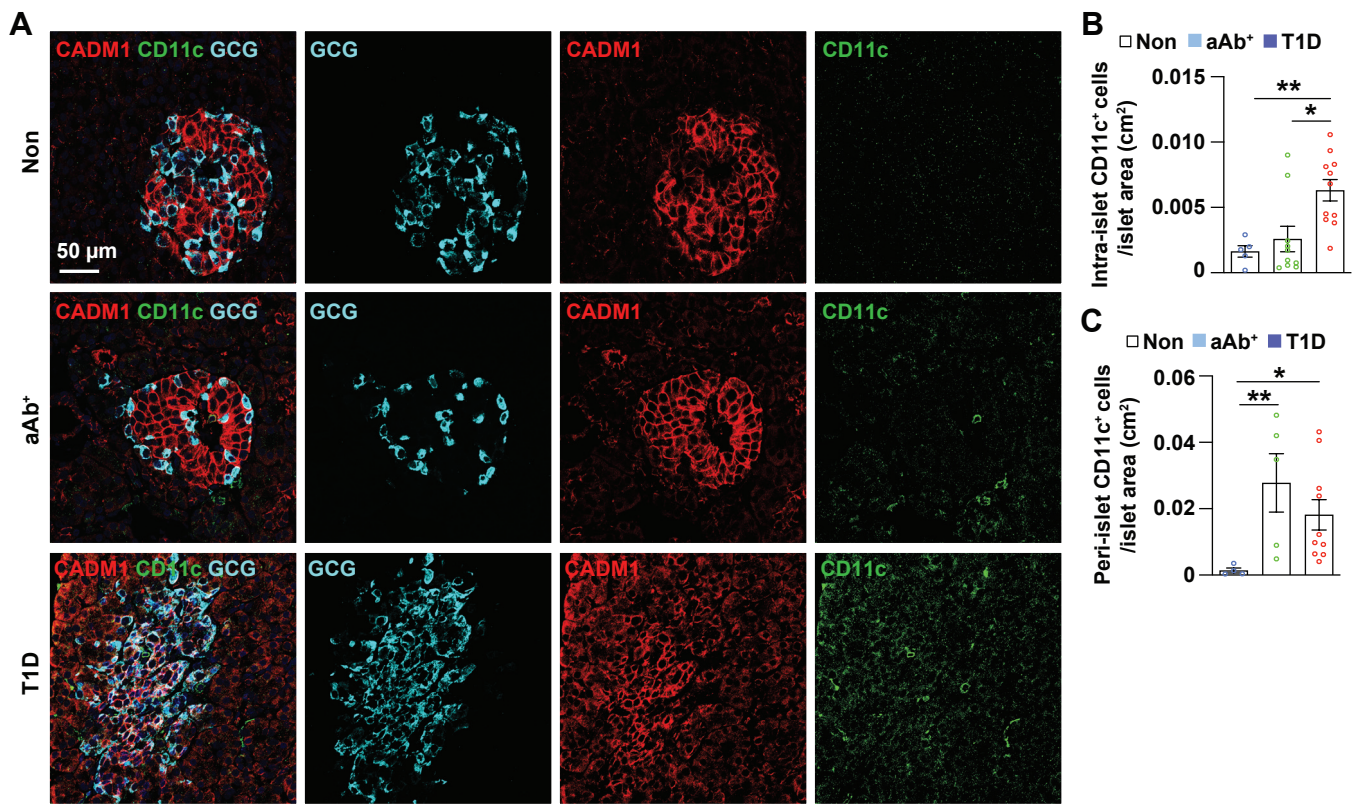**Supplemental Figure 1. Single-cell analysis revealed novel markers in islet-infiltrating cells during diabetes development.** Violin plots representing the (**A**) number of genes per cell, (**B**) mitochondrial genes percentage of all cells before QC, and (**C**) number of unique molecular identifiers (UMIs) before filtering and clustering. Colored lines indicate the filtering parameter values set for each sample (q indicates quartile). (**D**) Harmony integration of pancreatic islet cells pooled together from 4, 8, and 15-week-old NOD mice. (**E**) Feature plots of expression distribution for selected cluster-specific genes. Expression levels for each cell are color-coded and overlaid onto UMAP plot. (**F**) Top 5 marker genes for the 20 identified clusters. The dot size represents the percentage of cells within a group with an expression level > 0 and color-scale represents the average expression level (row Z-score) across all cells within the cluster.

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Supplemental Figure 1

Supplemental Figure 2. Control immunostaining for human pancreata from nPOD repository. (**A**) Immunostaining of paraffin-embedded pancreata from non-diabetic (Non), auto-antibody positive (aAb⁺), and T1D human subjects for insulin (green), glucagon (red), and CD45 (cyan). Scale bar: 50 μm. (**B**) Quantification of number of islets with >15 CD45⁺ cells within the islet periphery per mm² pancreas from Non, aAb⁺, and T1D human subjects. (**C**) Quantification of number of insulin⁺ cells per mm² pancreas from Non, aAb⁺, and T1D human subjects. (**D**) Quantification of number of glucagon⁺ cells per mm² pancreas from Non, aAb⁺, and T1D human subjects. (**E**) Quantification of number of CD45⁺ cells per mm² pancreas from Non, aAb⁺, and T1D human subjects. (**F**) Quantification of number of CD45⁺ cells adjacent to insulin⁺ or glucagon⁺ cells in pancreata of Non, aAb⁺, and T1D human subjects. (**G**) Representative images of immunostaining of glucagon (GCG) (red), insulin (green), and CD45 (cyan) in pancreata of Non, aAb⁺, and T1D human subjects. Scale bar: 100 μm. One-way ANOVA analysis has been performed using GraphPad Prism Software Version 7 for comparisons of three groups. Post hoc statistics were performed using Turkey's multiple comparisons test. Results are presented as mean ± S.E.M. *$P< 0.05$, **$P< 0.01$, ***$P< 0.001$.

Supplementary Figure 3. Increased number of CADM1⁺ cells adjacent to CD11c⁺ cells during T1D. (**A**) Immunostaining of paraffin-embedded pancreata from non-diabetic (Non), auto-antibody positive (aAb⁺), and T1D human subjects for CADM1 (red), glucagon (cyan) and CD11c (green). Scale bar: 50 µm. (**B**) Quantification of number of CD11c⁺ cells within the islet boundary per cm² endocrine pancreas of Non, aAb⁺, and T1D human subjects. (**C**) Quantification of number of CD11c⁺ cells at the islet periphery per cm² endocrine pancreas of Non, aAb⁺, and T1D human subjects. One-way ANOVA analysis has been performed using GraphPad Prism Software Version 7 for comparisons of three groups. Post hoc statistics were performed using Turkey's multiple comparisons test. Results are presented as mean ± S.E.M. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Supplemental Table 1. Demographic information of human pancreatic tissue donors from nPOD program and summary of available donor data including auto-antibody results: GADA, glutamic acid decarboxylase-65; IA-2A, islet antigen-2 or insulinoma antigen-2; ZnT8A, zinc transporter 8; mIAA, insulin autoantibodies. Insulin autoantibody (mIAA) is an important marker of islet autoimmunity and is utilized in confirmation of type 1 diabetes diagnosis; however, assay specificity after a person has been on exogenous insulin for more than 10 days, is no longer able to distinguish insulin autoantibodies from insulin antibodies which form in over 40% of patients treated with subcutaneous insulin (Fineberg et al. *Diabetologia* (1983)). Therefore, mIAA is not a reliable marker of autoimmunity after a donor has been on insulin therapy for more than 10 days.

nPOD CaseID	RRID	Donor Type ID	Auto-antibody_Results	Age (yr)	Duration of diabetes (yrs)	Gender	Race	BMI (kg/m2)	HbA1c	C-peptide	Cause of death
6310	SAMN15879364	Autoab Pos	GADA+	28	-	Female	Hispanic/Latino	22.4	n/a	10.54	Anoxia
6314	SAMN15879368	Autoab Pos	GADA+	21	-	Male	Caucasian	23.8	n/a	1.49	Head Trauma
6424	SAMN15879477	Autoab Pos	GADA+, mIAA+	17.65	-	Male	Caucasian	51.4	5.8	6.97	Head Trauma
6429	SAMN15879482	Autoab Pos	GADA+, mIAA+	22.1	-	Male	African Am	19.6	5.5	2.25	Head Trauma
6450	SAMN15879503	Autoab Pos	GADA+, ZnT8A+	22	-	Female	Caucasian	24.4	5.7	5.47	Anoxia
6512	SAMN15879564	Autoab Pos	IA2A+, mIAA+, ZnT8A+	30.59	-	Female	Caucasian	38.8	5.2	3.2	Cerebrovasc./Stroke
6517	SAMN18053201	Autoab Pos	GADA+	22.14	-	Male	Caucasian	26.6	5.6	9.74	Cerebrovasc./Stroke
6521	SAMN18053204	Autoab Pos	GADA+, IA-2A+, ZnT8A+	19.77	-	Male	Hispanic/Latino	24.1	5.8	7.44	Head Trauma
6148	SAMN15879204	T1D	GADA+, mIAA+	17.1	7	Male	Caucasian	23.9	n/a	<0.05	Anoxia
6195	SAMN15879251	T1D	GADA+, Ia-2A+, mIAA+, ZnT8A+	19.3	5	Male	Caucasian	23.7	n/a	<0.05	Head Trauma
6480	SAMN15879533	T1D	IA2A+, mIAA+	17.18	2.5	Male	Caucasian	27.0	10.2	0.13	Diabetic ketoacidosis
6526	SAMN18053209	T1D	IA2A+, mIAA+	29.74	1	Male	Hispanic/Latino	23	6.6	0.07	Anoxia
6524	SAMN18053207	T1D	GADA+, Ia-2A+, mIAA+, ZnT8A+	20.07	8	Male	Caucasian	29.5	6.5	0.03	Head Trauma
6520	SAMN18053203	T1D	GADA+, Ia-2A+, ZnT8A+	21.61	0	Male	Caucasian	29.3	11.9	0.37	Cerebrovasc./Stroke
6449	SAMN15879502	T1D	IA-2A+, mIAA+, ZnT8A+	24	2	Male	Caucasian	23	10.2	0.03	Head Trauma
6399	SAMN15879452	T1D	GADA+, IA-2A+, ZnT8A+	17.42	0	Male	Caucasian	32	10.4	1.41	Anoxia
6098	SAMN15879155	No diabetes	negative	17.8	-	Male	Caucasian	22.8	4.9	1.41	Head Trauma
6174	SAMN15879230	No diabetes	negative	20.9	-	Male	Caucasian	19.5	n/a	3	Cerebrovasc./Stroke
6389	SAMN15879442	No diabetes	negative	18.6	-	Male	Caucasian	20.93	5.1	7.22	Head Trauma
6516	SAMN18053200	No diabetes	negative	20.75	-	Male	Caucasian	28.8	5.5	8.91	Head Trauma
6492	SAMN15879545	No diabetes	negative	28.56	-	Male	Hispanic/Latino	26.6	6.2	2.13	Head Trauma
6509	SAMN15879561	No diabetes	negative	18.72	-	Male	Caucasian	25.8	5.4	2.21	Head Trauma
6479	SAMN15879532	No diabetes	negative	21.67	-	Female	Hispanic/Latino	20.9	5	1.74	Anoxia
6229	SAMN15879285	No diabetes	negative	31	-	Female	Caucasian	26.9	5.5	6.23	Head Trauma

Supplemental Table 2. Summary of statistical analyses. All statistical analysis for each figure including n numbers for each test cohort, statistical test performed, and resulting P values for all comparisons.

Figure	Sample size (n)	Statistical Test	Values
3C	ND (n=7) aAb+ (n=9) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=3.602, P =0.0432 Multiple comparison: ND vs aAb$^+$: P=0.3466 ND vs T1D: P=0.0344 T1D vs aAb$^+$: P=0.4014
3D	ND (n=14) aAb+ (n=12) T1D (n=11)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=40.55, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.0002 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=0.0004
4B	ND (n=17) aAb+ (n=15) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F = 15.07, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.0026 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=0.1168
4C	ND (n=17) aAb+ (n=15) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=16.01, P<0.0001 Multiple comparison: ND vs aAb$^+$: P<0.0001 ND vs T1D: P=0.0001 T1D vs aAb$^+$: P=0.9808
4D	ND (n=13) aAb+ (n=14) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=12.78, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.1074 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=0.0085
4E	ND (n=7) aAb+ (n=6) T1D (n=7)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=12.44, P=0.0005 Multiple comparison: ND vs aAb$^+$: P=0.048 ND vs T1D: P=0.0003 T1D vs aAb$^+$: P=0.0996
5B	ND (n=12) aAb+ (n=12) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=77.35, P<0.0001 Multiple comparison: ND vs aAb$^+$: P<0.0001 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=0.0061
5C	ND (n=10) aAb+ (n=12) T1D (n=14)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=37.79, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.0002 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=0.0006
5D	ND (n=7) aAb+ (n=8) T1D (n=9)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=11.38, P=0.0004 Multiple comparison: ND vs aAb$^+$: P=0.003 ND vs T1D: P=0.0005 T1D vs aAb$^+$: P=0.7949
6B	ND (n=3) aAb+ (n=10) T1D (n=11)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=4.340, P=0.028 Multiple comparison: ND vs aAb$^+$: P=0.0375 ND vs T1D: P=0.0275 T1D vs aAb$^+$: P=0.9853
6C	ND (n=9) aAb+ (n=9) T1D (n=9)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=12.64, P=0.0002 Multiple comparison: ND vs aAb$^+$: P=0.034 ND vs T1D: P=0.0001 T1D vs aAb$^+$: P=0.0762
6E	ND (n=6) aAb+ (n=3) T1D (n=3)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=24.62, P=0.0002 Multiple comparison: ND vs aAb$^+$: P=0.0002 ND vs T1D: P=0.0094 T1D vs aAb$^+$: P=0.0748
6F	ND (n=6) aAb+ (n=3) T1D (n=3)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=16.32, P=0.001 Multiple comparison: ND vs aAb$^+$: P=0.0021 ND vs T1D: P=0.0046 T1D vs aAb$^+$: P=0.8829

7C	ND (n=5) aAb+ (n=5) T1D (n=5)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F = 0.1505, P>0.9999 Distance: F = 0.1843, P>0.9999 Genotype: F =1310, P<0.0001
7D	ND (n=5) aAb+ (n=5) T1D (n=5)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F = 0.03389, P>0.9999 Distance: F = 0.03359, P>0.9999 Genotype: F =983, P<0.0001
8C	ND (n=10) aAb+ (n=11) T1D (n=11)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=12.45, P=0.0001 Multiple comparison: ND vs aAb$^+$: P=0.0049 ND vs T1D: P=0.0001 T1D vs aAb$^+$: P=0.3192
Suppl.2B	ND (n=12) aAb+ (n=3) T1D (n=7)	Ordinary one-way ANOVA Turkey's multiple comparisons test	summary: F = 7.330, P = 0.0044 Multiple comparison: ND vs aAb$^+$: P=0.5485 ND vs T1D: P=0.0031 T1D vs aAb$^+$: P=0.2516
Suppl.2C	ND (n=9) aAb+ (n=7) T1D (n=3)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=5.686, P=0.0136 Multiple comparison: ND vs aAb$^+$: P=0.2636 ND vs T1D: P=0.0113 T1D vs aAb$^+$: P=0.1382
Suppl.2D	ND (n=10) aAb+ (n=10) T1D (n=7)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=33.11, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.0075 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P<0.0001
Suppl.2E	ND (n=11) aAb+ (n=15) T1D (n=15)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=13.95, P<0.0001 Multiple comparison: ND vs aAb$^+$: P=0.2665 ND vs T1D: P=0.0006 T1D vs aAb$^+$: P=0.0018
Suppl.2F	ND (n=4) aAb+ (n=12) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=12.67, P=0.0002 Multiple comparison: ND vs aAb$^+$: P=0.0007 ND vs T1D: P<0.0001 T1D vs aAb$^+$: P=5128
Suppl.3B	ND (n=5) aAb+ (n=10) T1D (n=11)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=7.513, P=0.0031 Multiple comparison: ND vs aAb$^+$: P=0.7957 ND vs T1D: P=0095 T1D vs aAb$^+$: P=0.0106
Suppl.3C	ND (n=4) aAb+ (n=5) T1D (n=10)	Ordinary one-way ANOVA Turkey's multiple comparisons test	Summary: F=3.644, P=0.0497 Multiple comparison: ND vs aAb$^+$: P=0.0411 ND vs T1D: P=0.1618 T1D vs aAb$^+$: P=0.4723
Suppl.Table 1	ND (n=8) aAb+ (n=8) T1D (n=8)	Two-tailed unpaired Student's t-tes	ND vs aAb$^+$: t=1.243, P=0.2344 ND vs T1D: t=1.426, P=0.1758 T1D vs aAb$^+$: t=0.6131, P=0.5496