Cell Reports, Volume *39*

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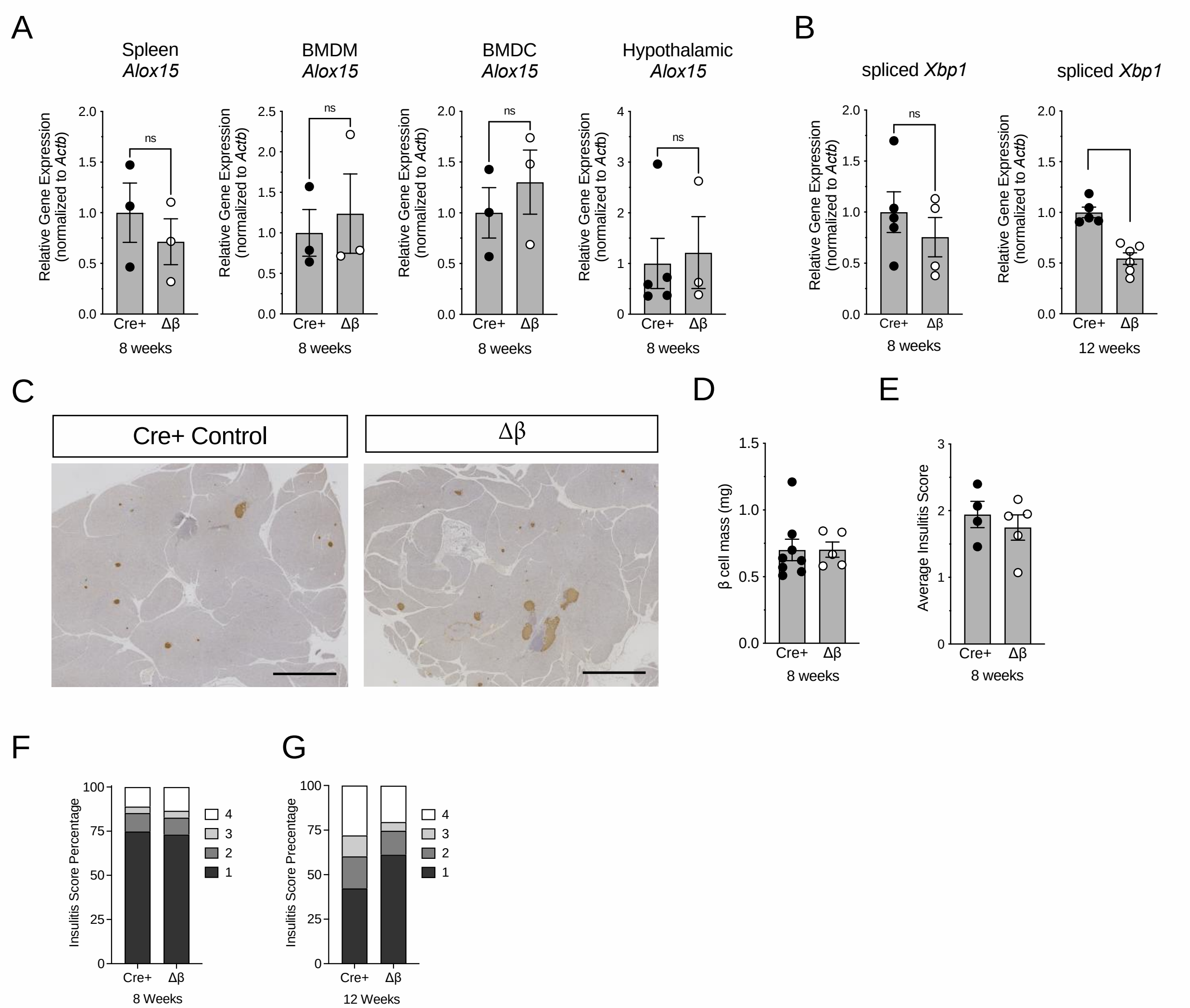
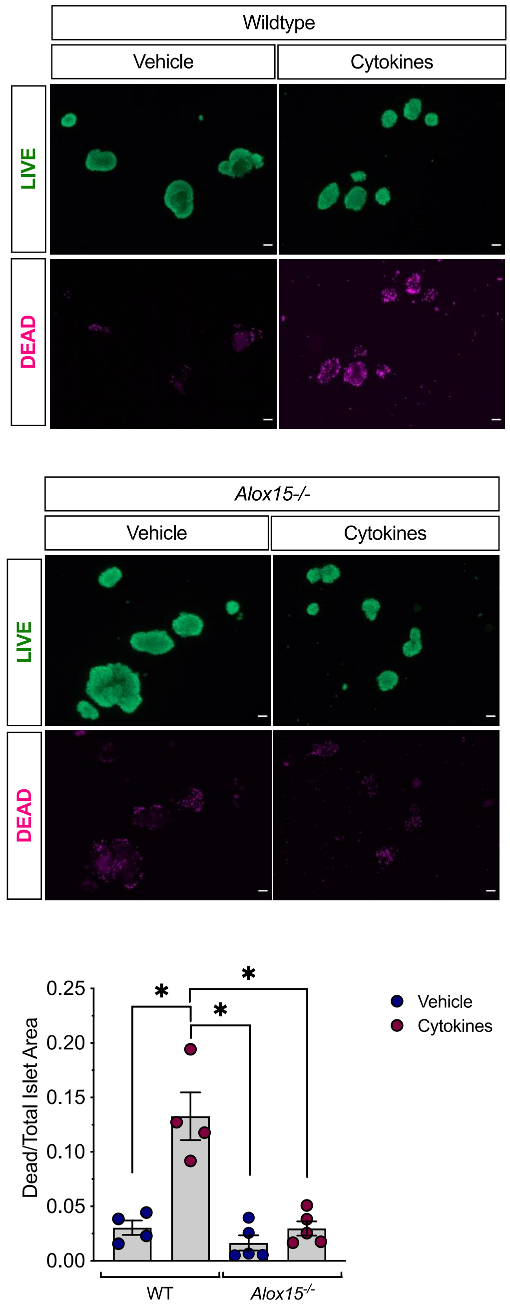
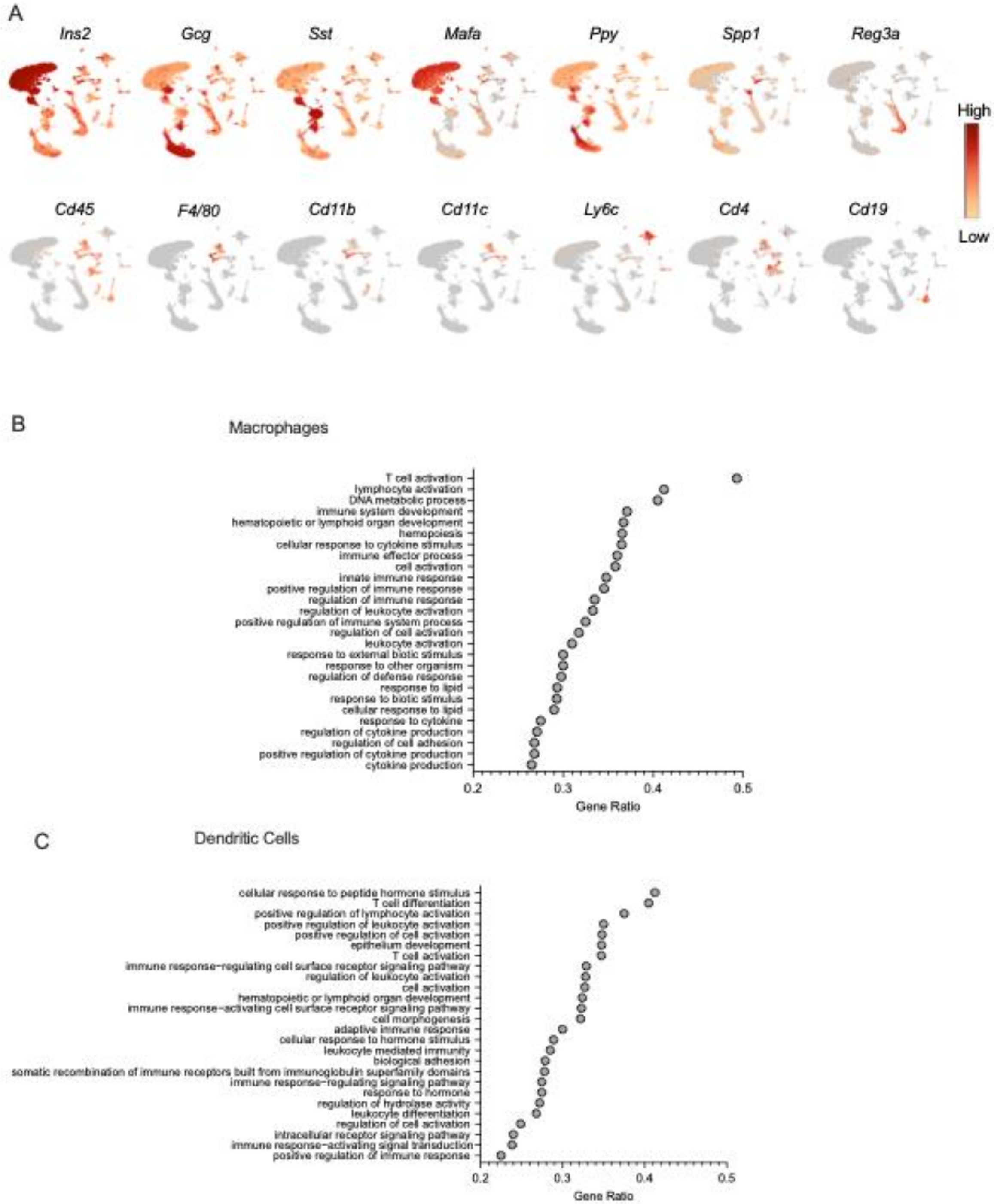


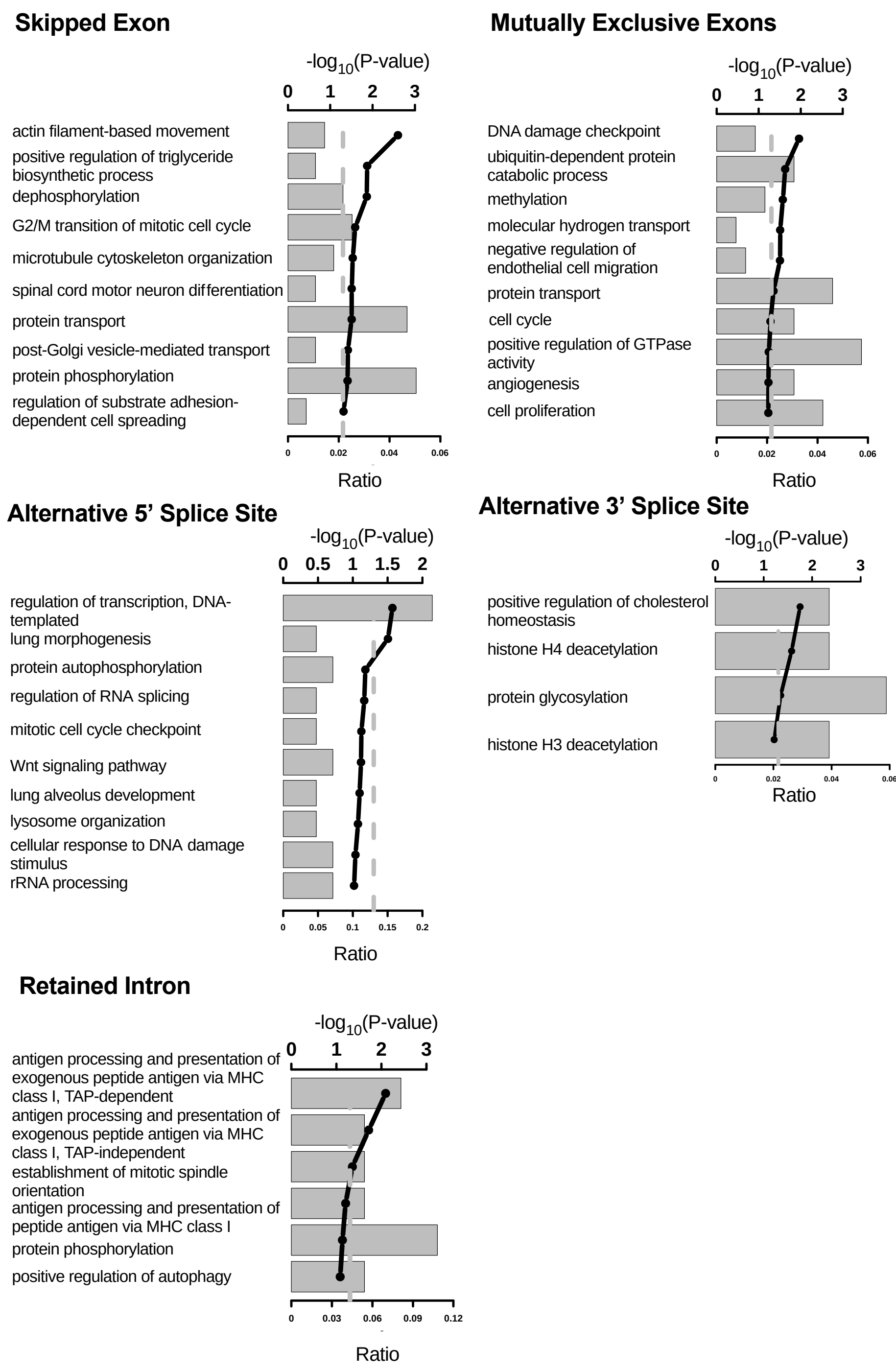
Supplemental Figure S1: β cell-specific deletion of Alox15 protects against development of T1D in NOD mice, related to Figure 2. *NOD-Alox15loxp/+* mice were crossed with *NOD-Pdx1PB-CreERTM* mice to generate *NOD-Cre+* and *NOD-Δβ* mice. At 6 weeks of age, the mice were administered 3 daily intraperitoneal injections of 2.5 mg of tamoxifen. (A) Quantitative RT-PCR from RNA isolated from the spleen, BMDM (bone marrow-derived macrophages), BMDC (bone marrow-derived dendritic cells), or hypothalamus at 8 weeks of age for *Alox15*. (B) Quantitative RT-PCR from isolated islets at 8 or 12 weeks of age for spliced *Xbp1*. (C) Images of whole pancreatic sections from representative mice at 8 weeks of age, immunostained for insulin (*brown*) and counterstained with hematoxylin. Scale bars, 500 μm. (D) Quantification of β-cell mass. (E) Average insulitis score. (F) Insulitis score distribution percentage at 8 weeks of age. (G) Insulitis score distribution percentage at 12 weeks of age. Data are expressed as the mean ± SEM. *P <0.05.



Supplemental Figure S2: Knockout of Alox15 protected β cells from cytokine-induced death, related to Figure 2. Isolated islets were treated with and without cytokines mixture and live and dead cell area was quantitated. Representative images of islets from wildtype and *Alox15-/-* islets stained for live cells (*green*) and dead cells (*magenta*). Scale bars, 100 μm.



Supplemental Figure S3: Single-cell RNA-seq analysis of islets of control and NOD-Δβ mice, related to STARS methods, Figure 4, and Figure 5. Islets were isolated from *NOD-Cre+* and *NOD-Δβ* mice at 8 weeks of age, dissociated into single cells, and analyzed for scRNA-seq using 10x genomics. (A) Markers for 7 major populations of immune cells inside the islets: CD45, F4/80, CD11b, CD11c, Ly6C, CD4 and CD19. Color assignments represent levels of expression. (B,C) GO-GSEA analysis performed in macrophage and dendritic cell clusters.



Supplemental Figure S4: Gene ontology pathway analysis of alternatively spliced transcripts in cytokine-treated human islets, related to Figure 6. Publicly available data from human islets (N=10 donors) treated with proinflammatory cytokines or control conditions were subjected to Gene Ontology pathway analysis for each of 5 mRNA splicing modes. Shown are the major Gene Ontology pathways and their respective p values and gene ratios.

Supplemental Table S2: Human islet donor characteristics, related to STAR methods and Figure 6.

Donor ID	**Age (yr)**	**Sex**	**Ethnicity /Race**	**BMI**	**Cause of Death**	**History of Diabetes**	**Islet Source[1]**
RRID:SAMN19470079	39	M	White	27.6	Anoxia	No	IIDP; Scharp-Lacy
RRID:SAMN19591106	61	M	Hispanic/ Latino	29.3	Cerebrovascular Stroke	No	IIDP; So CA Islet Cell Resource Center
RRID:SAMN19897466	28	F	Hispanic/ Latino	24.7	Cerebrovascular Stroke	No	IIDP; University of Pennsylvania
RRID:SAMN19859645	58	M		27.4	Neurological	No	University of Alberta Islet Core
RRID:SAMN19796386	40	M		31.7	Neurological	No	University of Alberta Islet Core

[1]IIDP = Integrated Islet Distribution Program

Supplemental Table S3: Oligonucleotide sequences, Related to STAR Methods

Mouse Gene	***Sequence***
Actb Forward	5'-CCCTAGGCACCAGGGTGTGA-3'
Actb Reverse	5'-GCCATGTTCAATGGGGTACTTC-3'
Alox15 forward	5'-CTCTCAAGGCCTGTTCAGGA-3'
Alox15 reverse	5'-GTCCATTGTCCCCAGAACCT-3'
Atf4 forward	5'-GCAGTGTTGCTGTAACGGACA-3'
Atf4 reverse	5'-CGCTGTTCAGGAAGCTCATCT-3'
Cd274 forward	5'-GCATTATATTCACAGCCTGC-3'
Cd274 reverse	5'-CCCTTCAAAAGCTGGTCCTT-3'
Il10 forward	5'-TGCACTACCAAAGCCACAAG-3'
Il10 reverse	5'-TAAGAGCAGGCAGCATAGCA-3'
Il12 forward	5'-ATGACCCTGTGCCTTGGTAG-3'
Il12 reverse	5'-TCTCCCACAGGAGGTTTCTG-3'
Il1b forward	5'-AACCTGCTGGTGTGTGACGTTC-3'
Il1b reverse	5'-CAGCACGAGGCTTTTTTGTTGT-3'
Il6 forward	5'-GAGGATACCACTCCCAACAGACC-3'
Il6 reverse	5'-AAGTGCATCATCGTTGTTCATACA-3'
Ins1 forward	5'-AGCAAGCAGGTCATTGTTCC-3'
Ins1 reverse	5'-GACGGGACTTGGGTGTGTAG-3'
Mafa forward	5'-CCTGTAGAGGAAGCCGAGGAA-3'
Mafa reverse	5'-CCTCCCCCAGTCGAGTATAGC-3'
Pdx1 forward	5'-CGGACATCTCCCCATACGAAG-3'
Pdx1 reverse	5'-CCCCAGTCTCGGTTCCATTC-3'
Xpb1s forward	5'-CTGAGTCCGAATCAGGTGCAG-3'
Xpb1s reverse	5'-GTCCATGGGAAGATGTTCTGG-3'