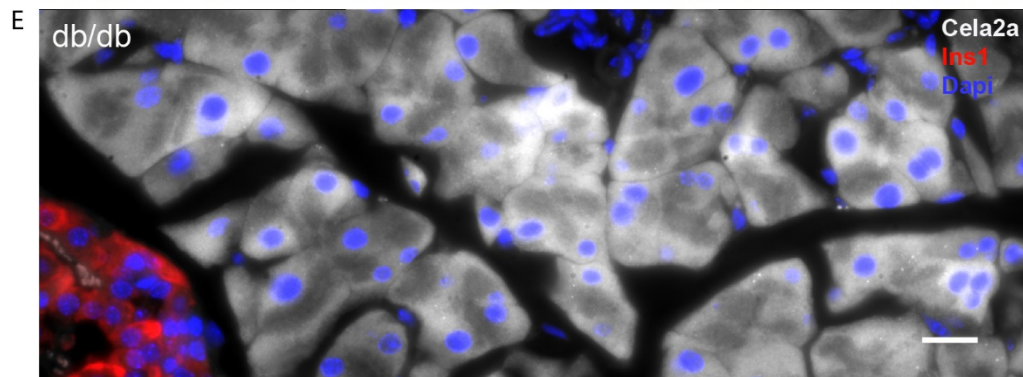
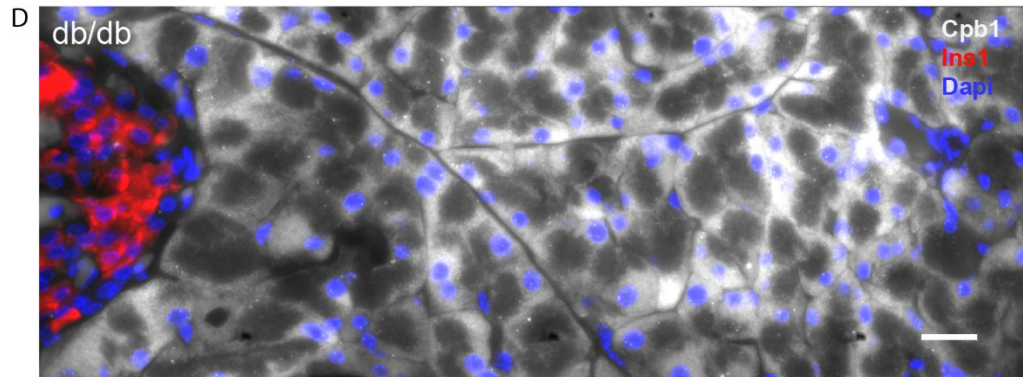
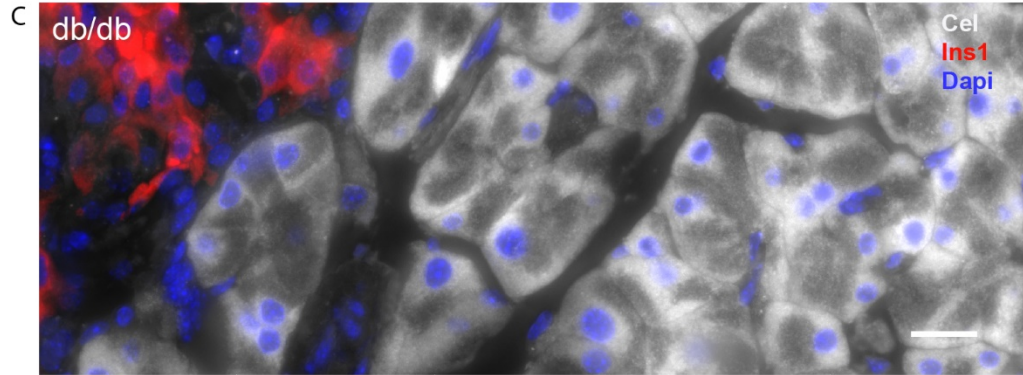
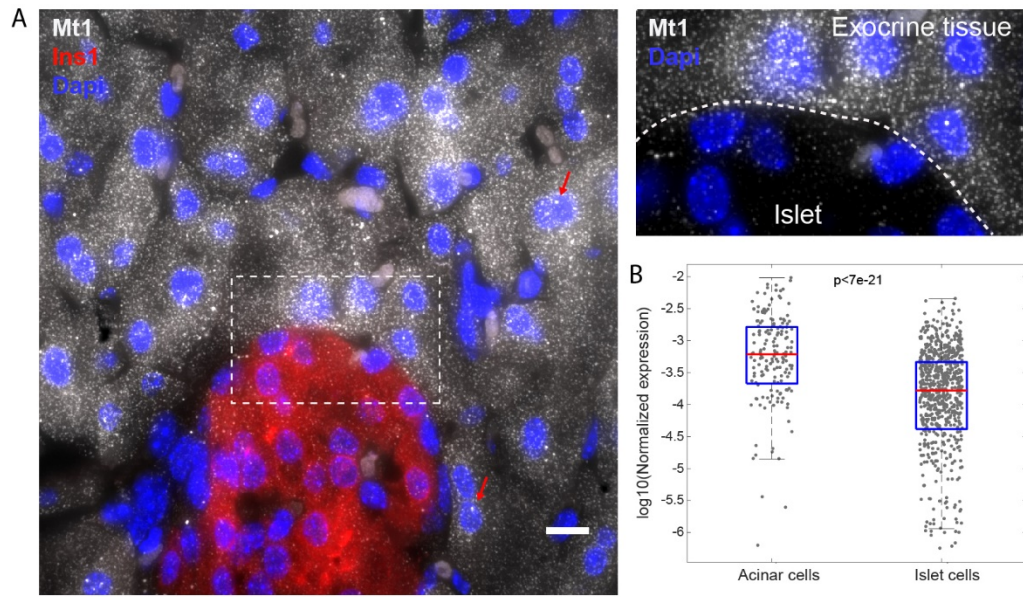


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Supplemental Information

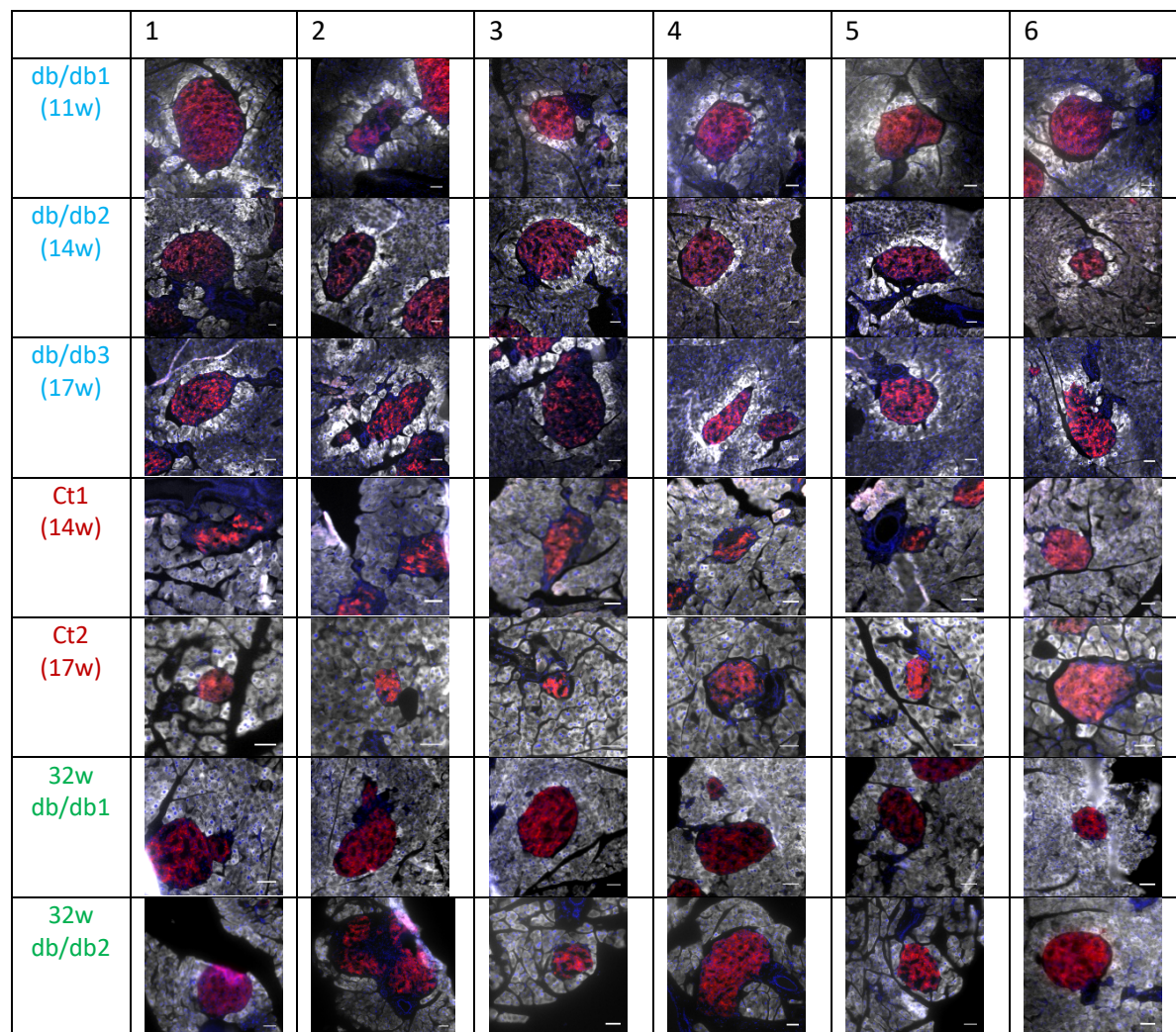
**Zonation of Pancreatic Acinar Cells
in Diabetic Mice**

Adi Egozi, Keren Bahar Halpern, Lydia Farack, Hagar Rotem, and Shalev Itzkovitz

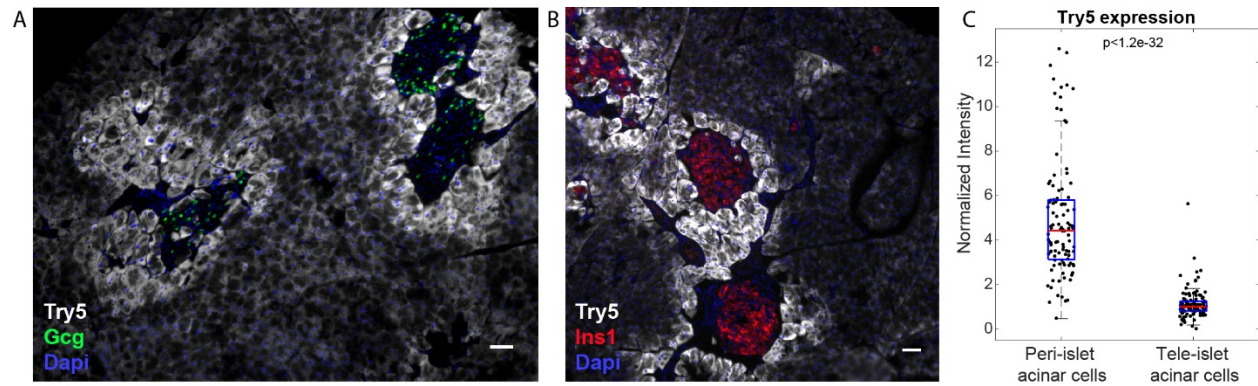


Supplementary Figure 1 – smFISH enables quantification of exocrine gene expression in the intact pancreas.

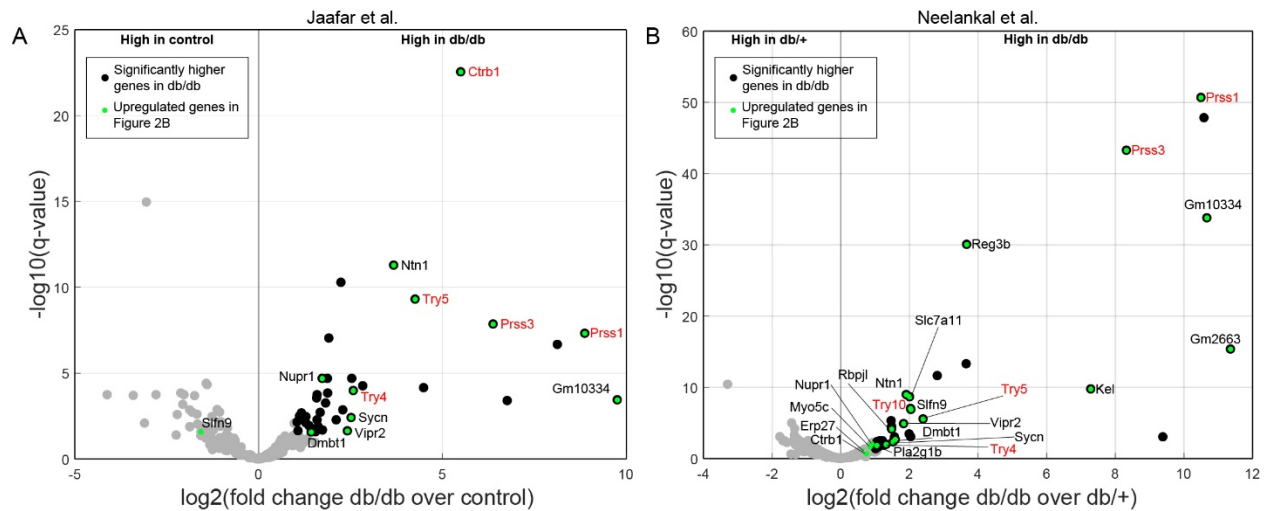
Related to Figure 1. A) smFISH image of *Mtl* mRNA (gray dots) reveals higher expression in acinar cells compared in islet cells (blowup). Red arrows mark transcription sites in the nuclei. B) Quantification of *Mtl* expression from the Tabula Muris single cell dataset (Tabula Muris Consortium et al., 2018) confirms higher expression in acinar cells compared to islet cells (3.7 fold change, $p < 7e-21$). Red lines are medians, blue boxes are 25-75 percentiles. C-E) smFISH images of *Cel* (C), *Cpb1* (D) and *Cela2a* (E) demonstrate non-zonated expression in db/db mice. *Ins1* mRNA in red, Dapi in blue, scale bar-10 μ m in A and 20 μ m in C-E.



Supplementary Figure 2 – Montage of *Try5* expression in representative islets from young db/db mice, controls and old db/db mice. Related to Figure 1 and Figure 3. For all images: *Try5* in gray, *Ins1* in red and Dapi in blue. Scale bars-50µm. Islets were selected based on size, regardless of *Try5* gene expression. Color scales are different for each panel and meant to demonstrate the relative intensity between peri-islet and tele-islet acinar cells within each slide.



Supplementary Figure 3 – peri-islet acinar zonation of Trypsin is recapitulated in the BKS.Cg-Dock7m^{+/+} Leprdb/J db/db mouse model. Related to Figure 1. smFISH images from two different 14 weeks old mice. A) *Try5* in gray, *Gcg* in green and Dapi in blue. B) *Try5* in gray, *Ins1* in red and Dapi in blue. Scale bars-50 μ m. C) *Try5* expression is significantly elevated in peri-islet acinar cells compared to tele-islet acinar cells in BKS.Cg-Dock7m^{+/+} Leprdb/J db/db mice (12 islets from 3 mice, $p < 1.2e-32$). Red lines are medians, blue boxes are 25-75 percentiles.



Supplementary Figure 4 – Induction of the peri-islet acinar expression program is similar in another dataset (Jaafar et al., 2019) and when considering db/db vs. db/+ mice (Neelankal John et al., 2018). Related to Figure 2. A) Differential gene expression between acinar transcripts of db/db islets vs. control islets in Jaafar et al. dataset (Jaafar et al., 2019). All genes elevated in Neelankal John et al. (Neelankal John et al., 2018) db/db islets, with the exception of *Slfn9*, are significantly elevated in this dataset as well. B) Differential gene expression between acinar transcripts in db/db islets vs. the heterozygote db/+ islets in Neelankal John et al. dataset (Neelankal John et al., 2018), showing the same set of induced genes as in the comparison with controls (Figure 2B). In both plots, black dots mark genes with $\log_2(\text{fold change}) > 1$ and $q\text{-value} < 0.05$. Green dots are the acinar genes that we found to be significantly induced in db/db islets from Neelankal John et al. (Neelankal John et al., 2018, Figure 2B). Red - trypsin genes.