

770 Supplementary Table 1. The primers used for quantitative RT-PCR.
 771

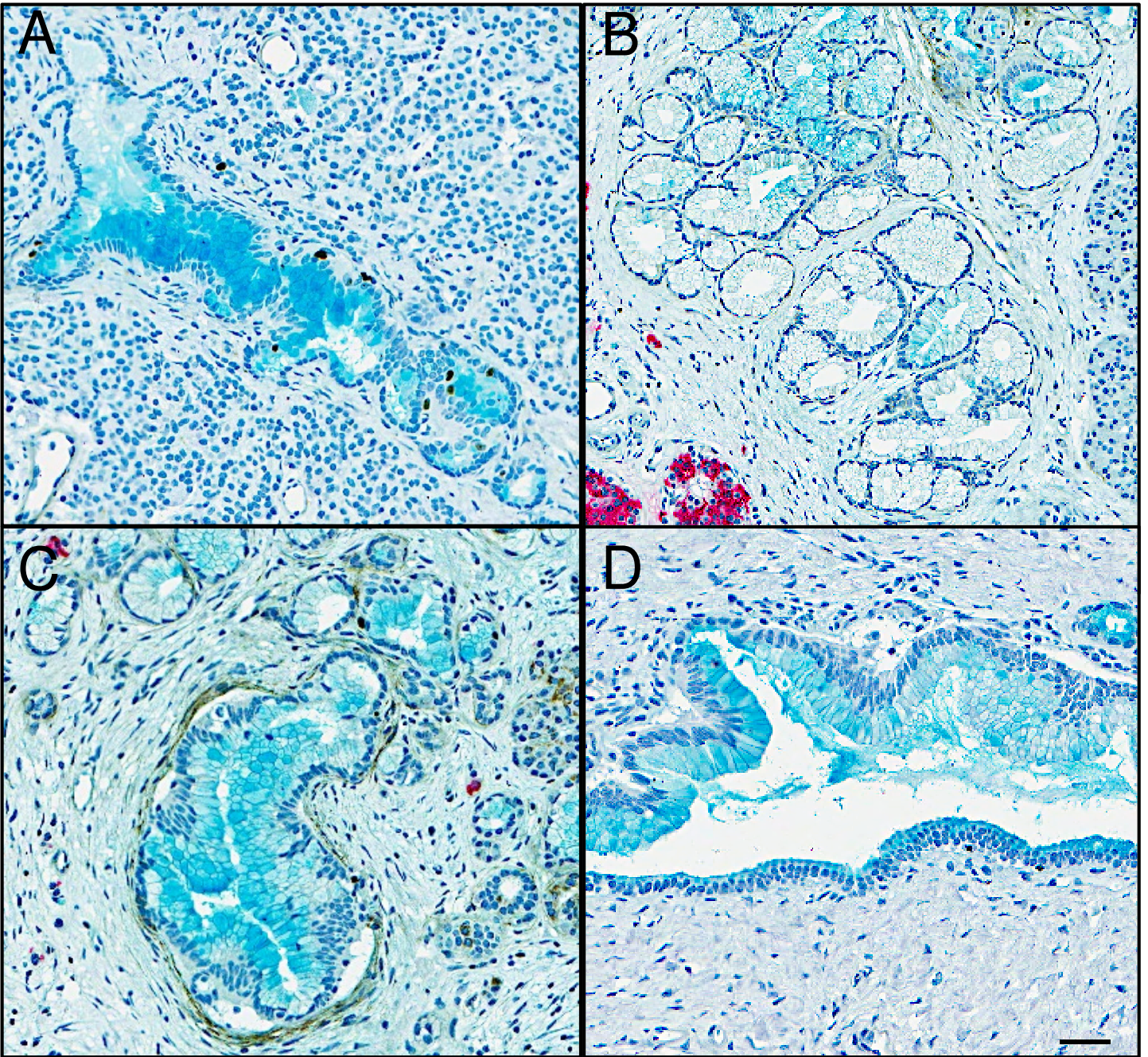
Gene name	Forward (5' > 3')	Reverse (5' > 3')
Human		
<i>CXCL1</i>	GCGCCCAAACCGAAGTCATA	ATGGGGGATGCAGGATTGAG
<i>PF4</i>	CCCCACTGCCCAACTGATAG	TTCTTGTACAGCGGGGCTTG
<i>CXCL10</i>	TGCCATTCTGATTTGCTGCC	TGCAGGTACAGCGTACAGTT
<i>GAPDH</i>	CCAGAACATCATCCCTGCCT	CCTGCTTCACCACCTTCTTG
Rat		
<i>Cxcl1</i>	GCCACACTCAAGAATGGTCG	TGGGGACACCCTTTAGCATC
<i>Pf4</i>	CTGCTTCTTCTGGGTCTGCT	CCATTCTTCAGCGTGGCTAT
<i>Cxcl10</i>	TGCAAGTCTATCCTGTCCGC	TCTTTGGCTCACCGCTTTCA
<i>Gapdh</i>	ATGACTCTACCCACGGCAAG	CTGGAAGATGGTGATGGGTT

772

773 **SUPPLEMENTARY FIGURES**

774 **Supplementary Figure 1.** A-D. Examples of **pancreatic intraepithelial neoplasia (PanIN)** lesions
775 identified in **non-diabetic (ND)** individuals (A: donor 6034, low grade PanIN; B: donor 6097, low
776 grade PanIN; C: donor 6097, low grade PanIN, D: donor 6102, low grade PanIN; all images
777 acquired with a 20x lens (200x magnification)) stained for Alcian Blue to detect mucin deposition,
778 insulin (pink) and Ki67 (brown) to mark replicating cells. Scale bar = 50 μ m.

779

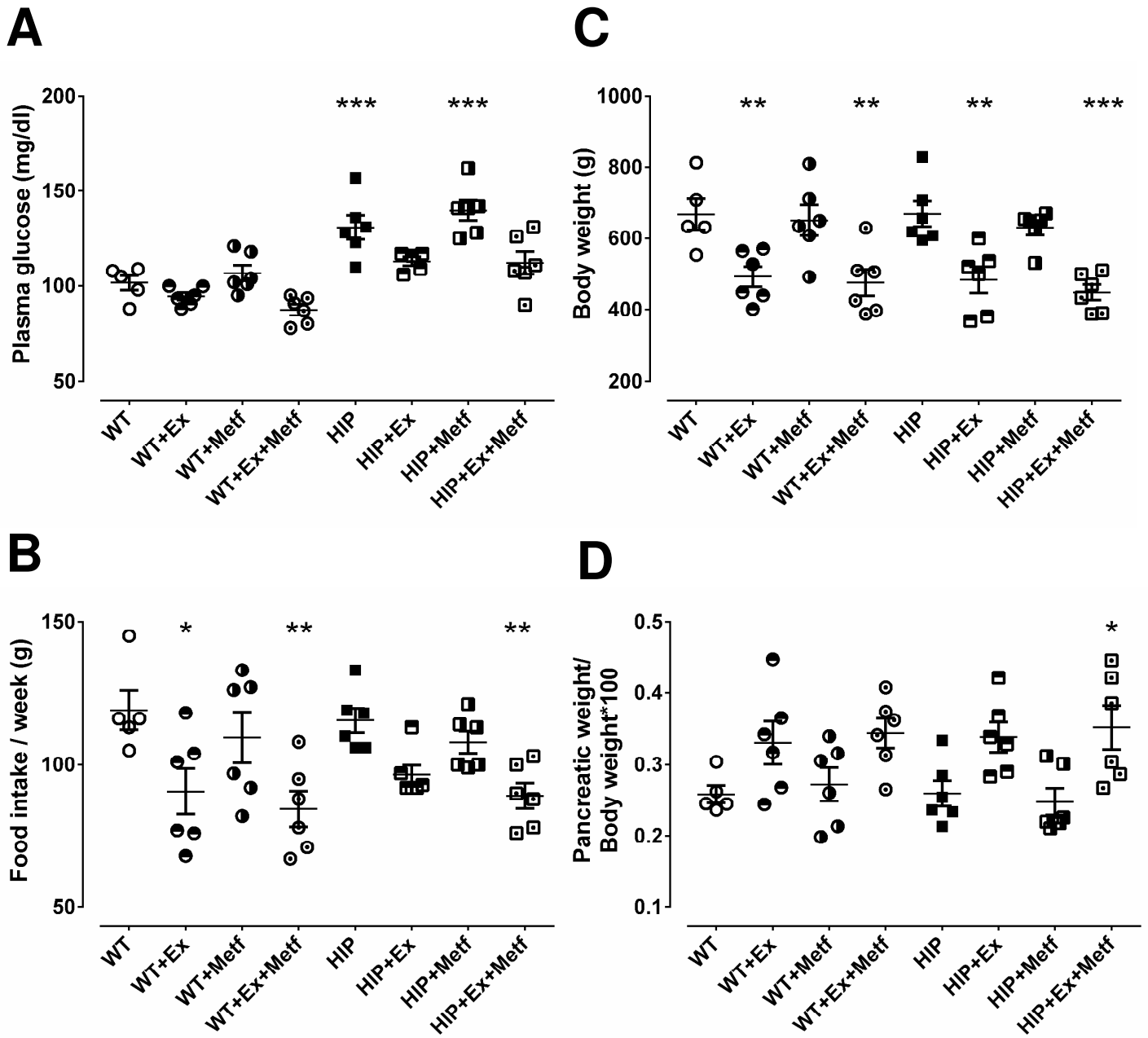


Supplementary Figure 1 Nondiabetic case examples of PanIns

780 **Supplementary Figure 2.** Plasma glucose (A), food intake (B), body weight (C) and pancreatic
781 weight/body weight*100 (D) in **human IAPP transgenic (HIP) and wild type (WT)** rats at age 12
782 weeks **treated or not with Exendin-4 (Ex), metformin (Metf) or combination of the two.** WT n=5,
783 WT+Ex n=6, WT+Metf n=6, WT+EX+Metf n=6, HIP n=6, HIP+Ex n=6, HIP+Metf n=6,
784 HIP+Ex+Metf n=6. **Data represent mean \pm SEM, one-way ANOVA Post Hoc Dunnett's test;**
785 ***p<0.05, **p<0.01, ***p<0.001.**

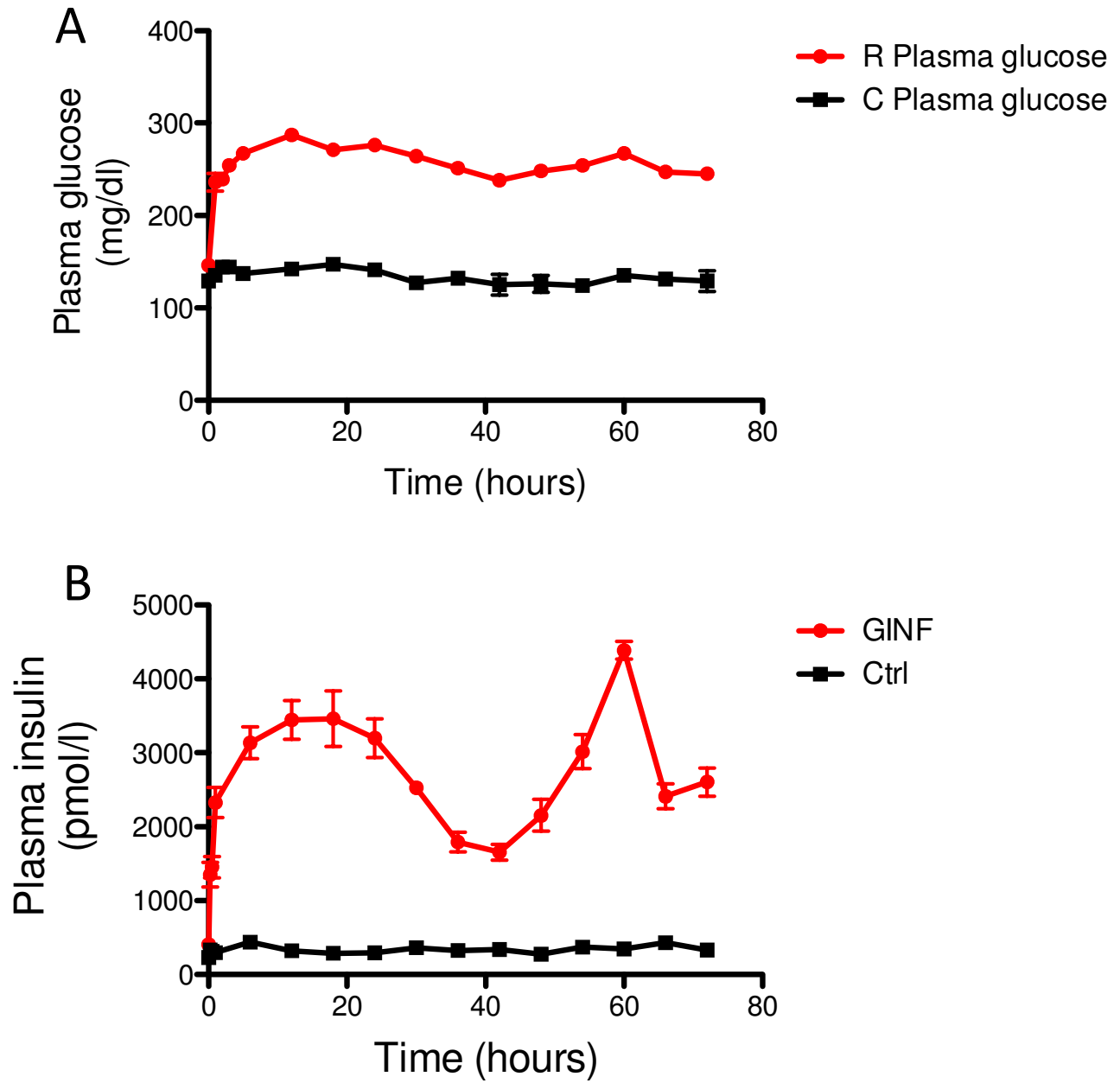
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Supp Figure 2



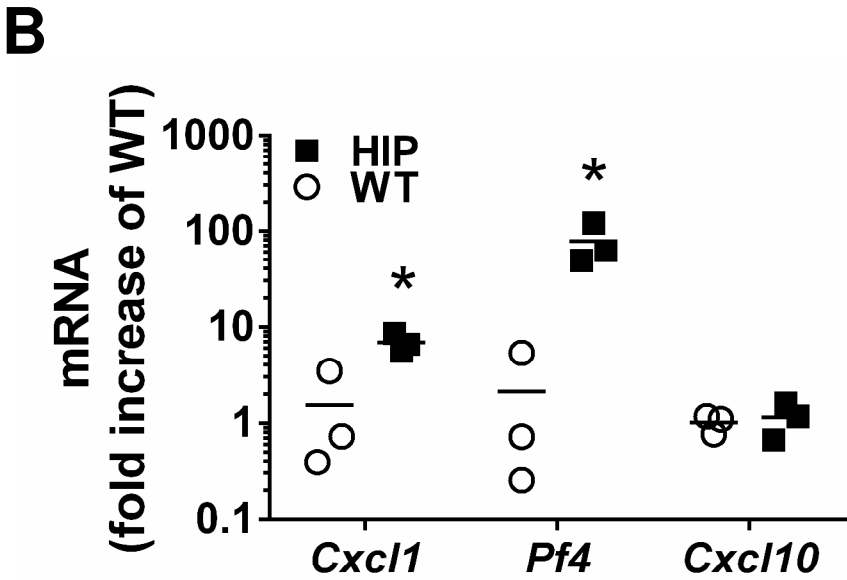
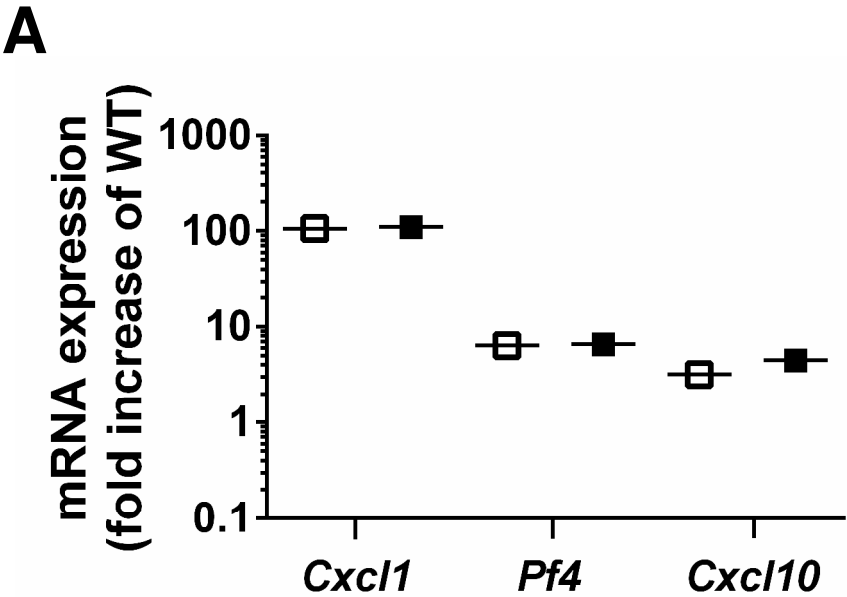
787 **Supplementary Figure 3.** 72-hour chronic glucose infusion (GINF). Plasma glucose (A) and
788 Plasma insulin (B) (R n=5, C n=3).
789

Supp Figure 3



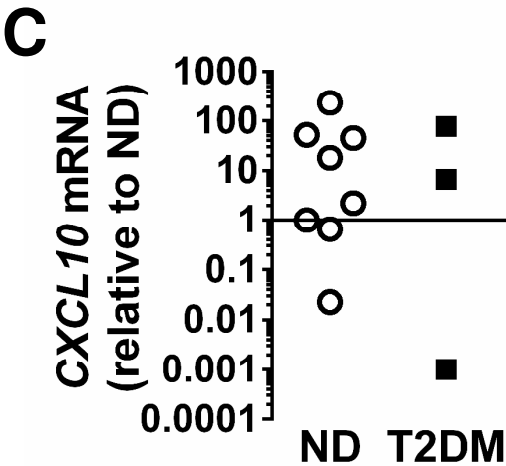
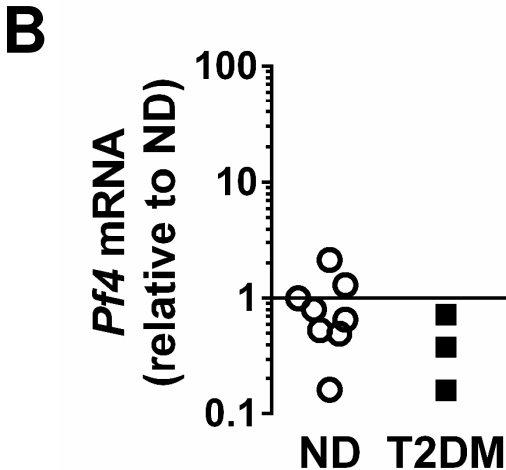
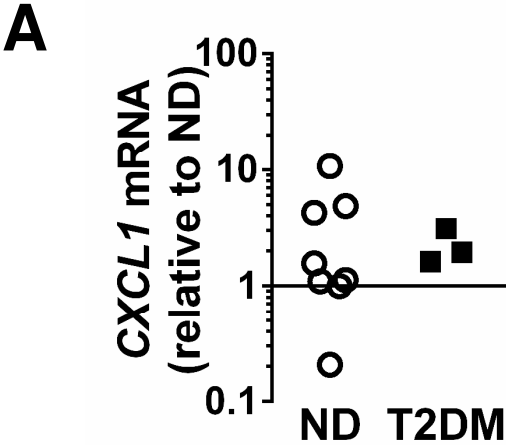
790 **Supplementary Figure 4.** (A) Fold increase in mRNA expression of *Cxcl1*, *Pf4* and *Cxcl10* (n=2)
791 in **human IAPP transgenic (HIP)** rat islets over wild type (WT) assessed by Microarray. (B) mRNA
792 levels of chemokines measured by quantitative RT-PCR. *Gapdh* was used as a housekeeping gene.
793 Quantification was made relative to the average of mRNA in WT. **Data represent mean \pm SEM;**
794 **n=3 rats per group; two tailed Student's t test, * p<0.05.**
795

Supp Figure 4

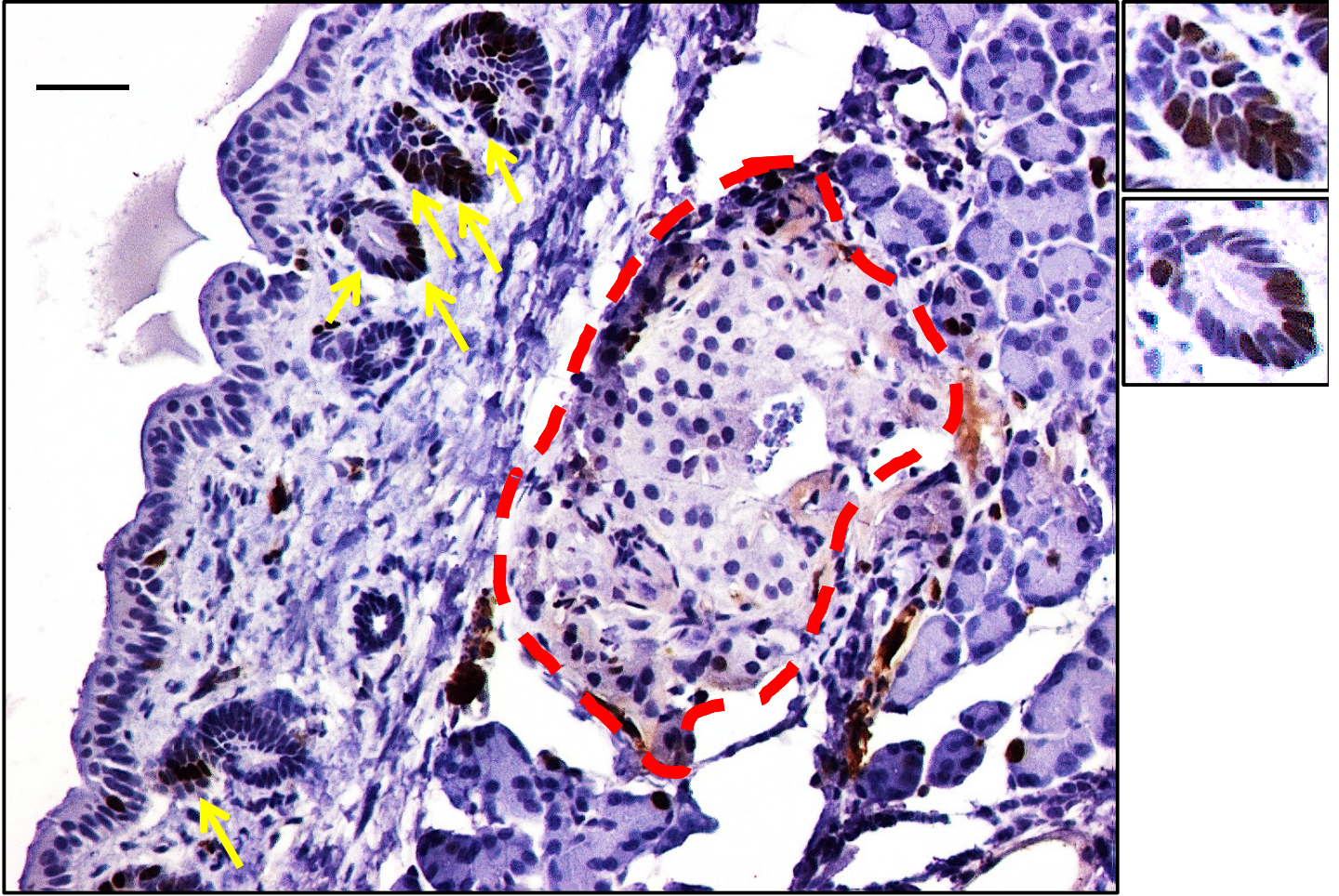


796 **Supplementary Figure 5.** Chemokine expression in human islets. *CXCL1* (A), *PF4* (B) and
797 *CXCL10* (C) mRNA expression in human islets from 3 **type 2 diabetes mellitus (T2DM)** subjects
798 (black **squares**) and 8 **non-diabetic (ND)** donors (white **circles**) measured by RT-qPCR; *GAPDH*
799 was used as a housekeeping gene. Quantification was made relative to a randomly chosen ND.
800

Supp Figure 5



801 **Supplementary Figure 6.** An example of an islet (circled in broken red line) adjacent to a ductal
802 compartment with a high frequency of replication in the **pancreatic duct gland (PDG)** compartment
803 (yellow arrows) in **a human IAPP transgenic (HIP)** rat. Insets show higher power examples of
804 replication in PDGs. Sections are stained for Ki67 with a hematoxylin counterstain. Insets show
805 higher power views of PDGs, showing Ki67 positive nuclei. Scale bar = 50 μ m.
806

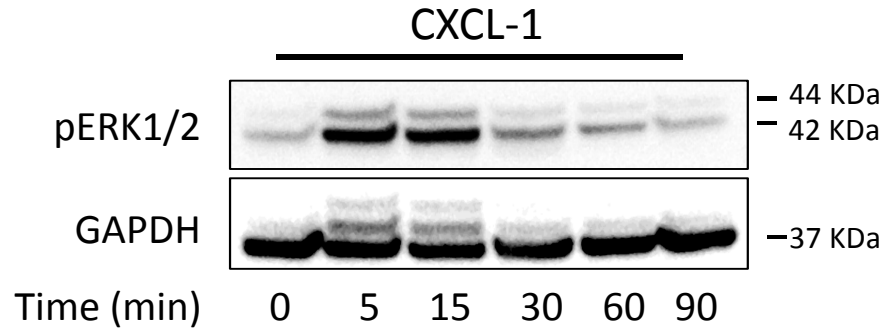


Supp Figure 6

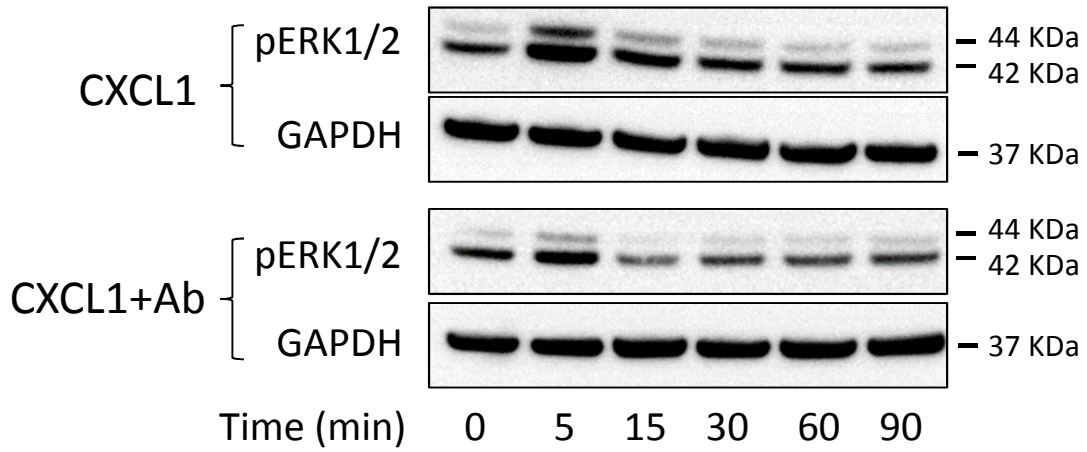
807 **Supplementary Figure 7.** Western Blot analysis showing a time-dependent phosphorylation of
808 the pro-proliferative MAP kinases ERK1/2 in **human pancreatic duct epithelial (HPDE)** cells
809 incubated with CXCL1 (A) and in the presence or absence of the anti-CXCL1 neutralizing mouse
810 monoclonal antibody (**clone MM0208-9A18, ab89318, Abcam, Cambridge, MA**) (B). CXCL1 and
811 CXCL1 mixture with antibody was pre-incubated for 1 h at 37 °C before addition to cells.
812

Supplemental Figure 7

A

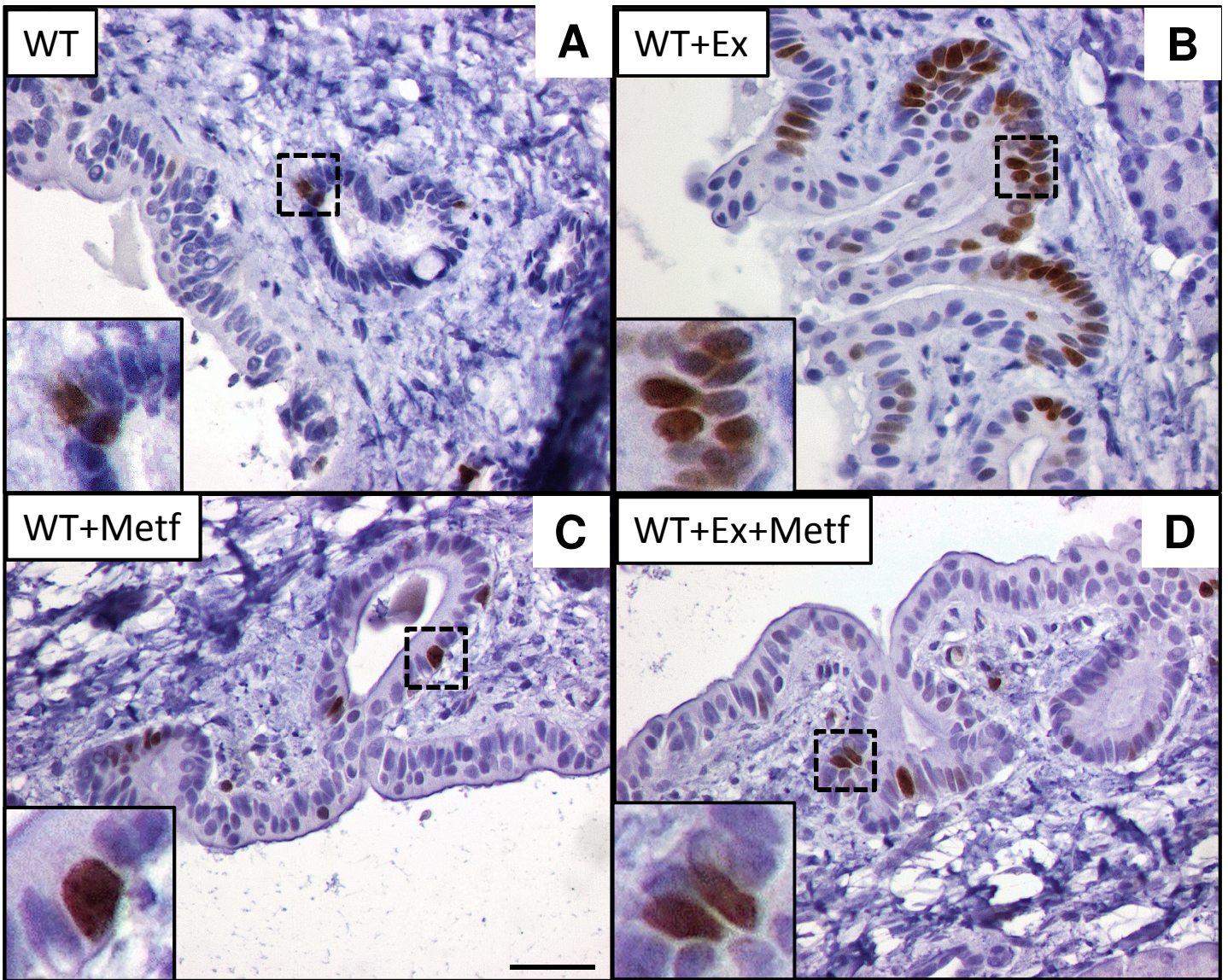


B



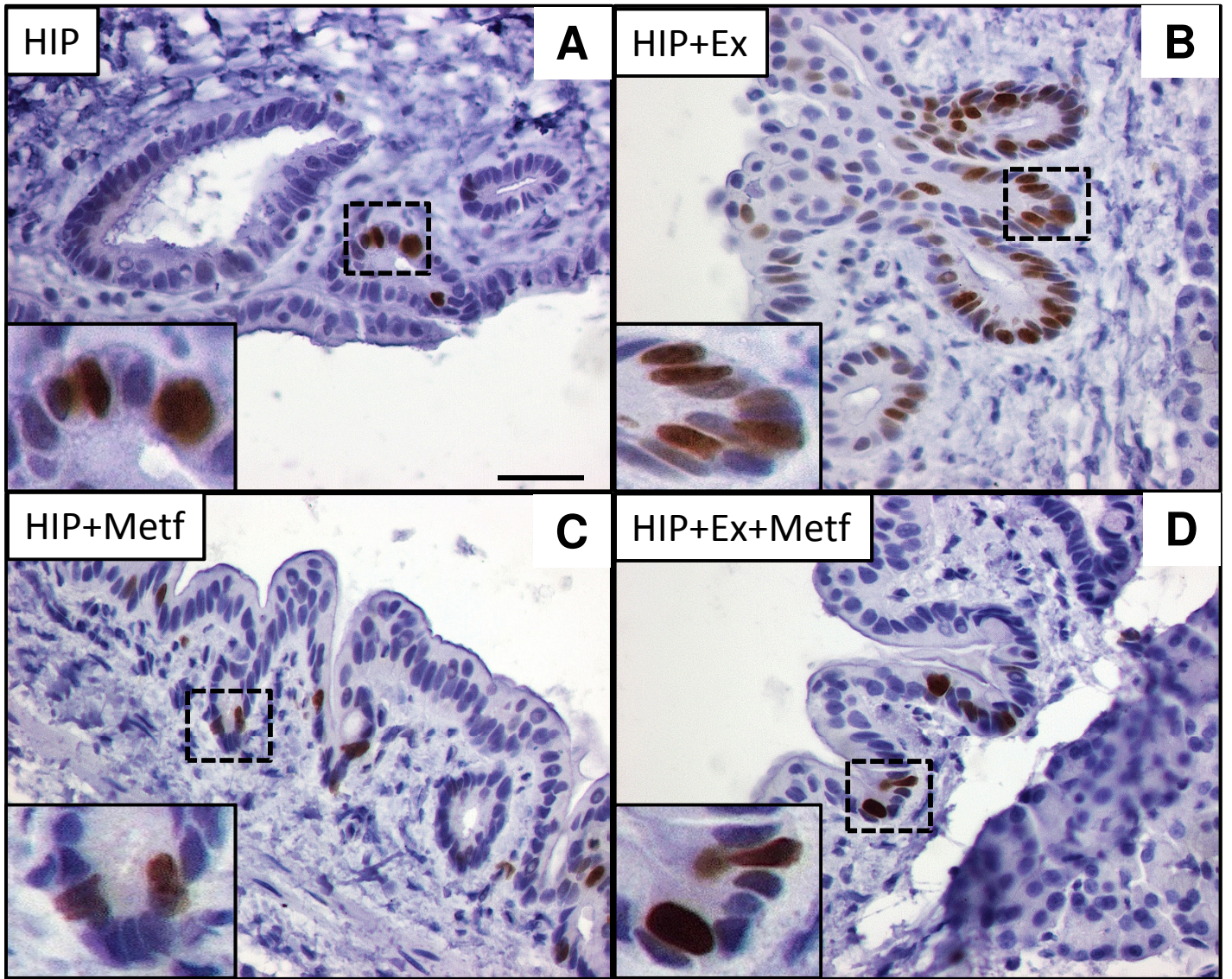
813 **Supplementary Figure 8.** Representative examples of replication in the **pancreatic duct gland**
814 **(PDG)** compartment in **wild type (WT)** rat (A) and WT rat treated with exendin-4 (B), metformin
815 (C) and exendin-4+metformin (D). Sections are stained for Ki67 and counterstained with
816 hematoxylin. Insets show higher power views of Ki67 positive nuclei in PDGs indicated by broken
817 square in the lower power image. Scale bar = 50µm.

818



Supplementary Fig 8 per reviewer

819 **Supplementary Figure 9.** Representative examples of replication in the **pancreatic duct gland**
820 **(PDG) compartment in human IAPP transgenic (HIP) rat (A)** and HIP rat treated with exendin-4
821 **(B), metformin (C) and exendin-4+metformin (D).** Sections are stained for Ki67 with a
822 hematoxylin counterstain. Insets show higher power views of Ki67 positive nuclei in PDGs
823 indicated by broken square in the lower power image of PDGs. Scale bar = 50 μ m.



Supplementary Fig 9 per reviewer