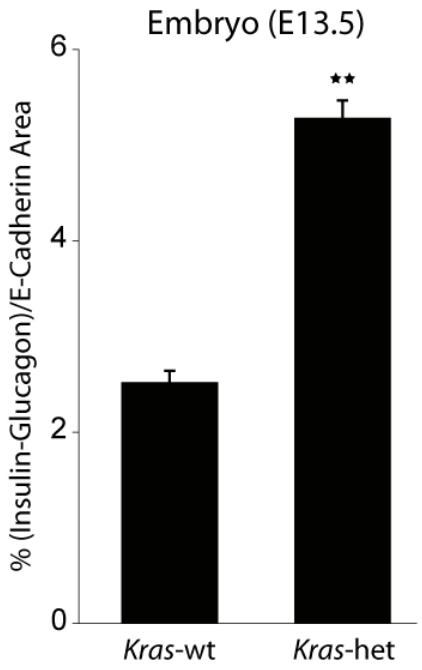
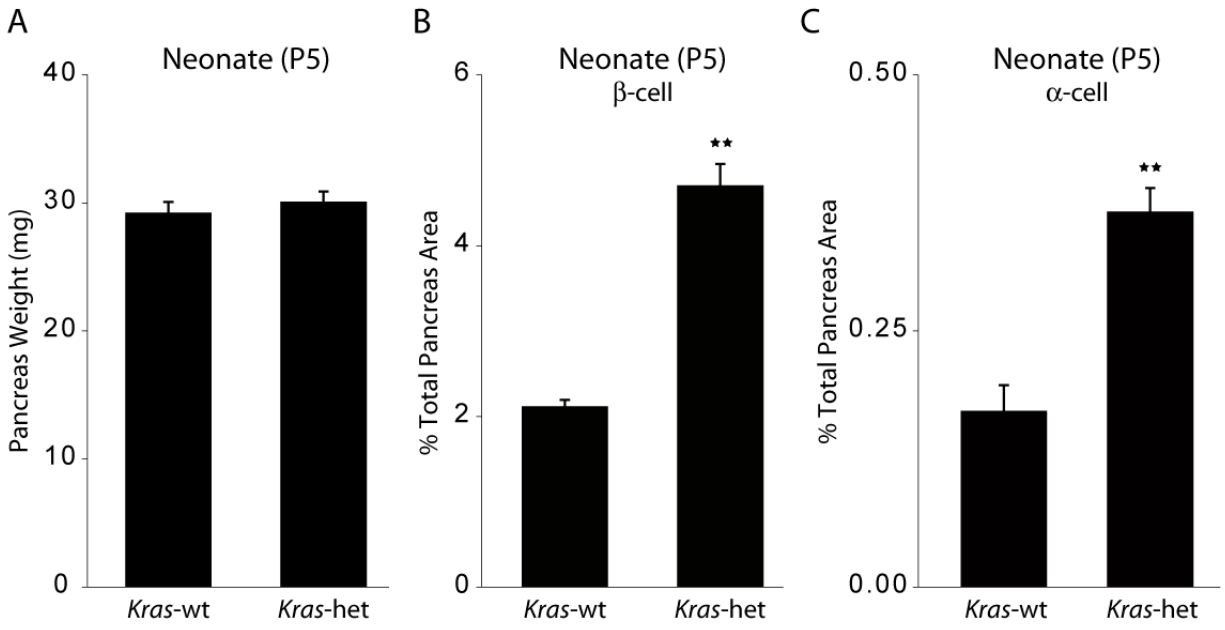
**Supplemental Data**



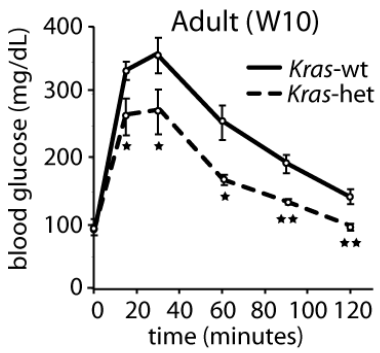

**Supplemental Figure 1**

Endocrine cell mass in the embryonic mouse pancreas. Percentage of Insulin-Glucagon immunostaining with respect to the epithelial pancreas (E-Cadherin) from E13.5 mouse embryos with the indicated genotypes (n=6 *Kras*-wt, n=6 *Kras*-het). All data points represent the mean ± SEM. **$p < 0.01$ vs. wild-type animals by two-tailed Student's t test.



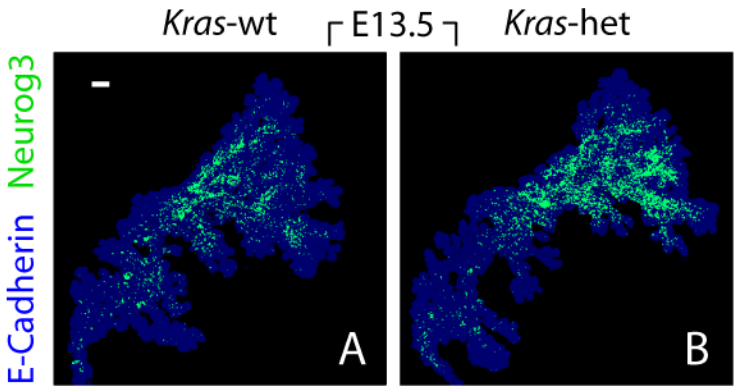

**Supplemental Figure 2**

Endocrine cell mass in the neonatal mouse pancreas. Quantification of the pancreas weights (**A**) and percentages of Insulin (**B**) and Glucagon (**C**) areas with respect to total pancreas (DAPI) from P5 mouse neonates with the indicated genotypes (n=3 *Kras*-wt, n=3 *Kras*-het). All data points represent the mean ± SEM. **$p < 0.01$ vs. wild-type animals by two-tailed Student's t test. Scale bars are 50 μm.



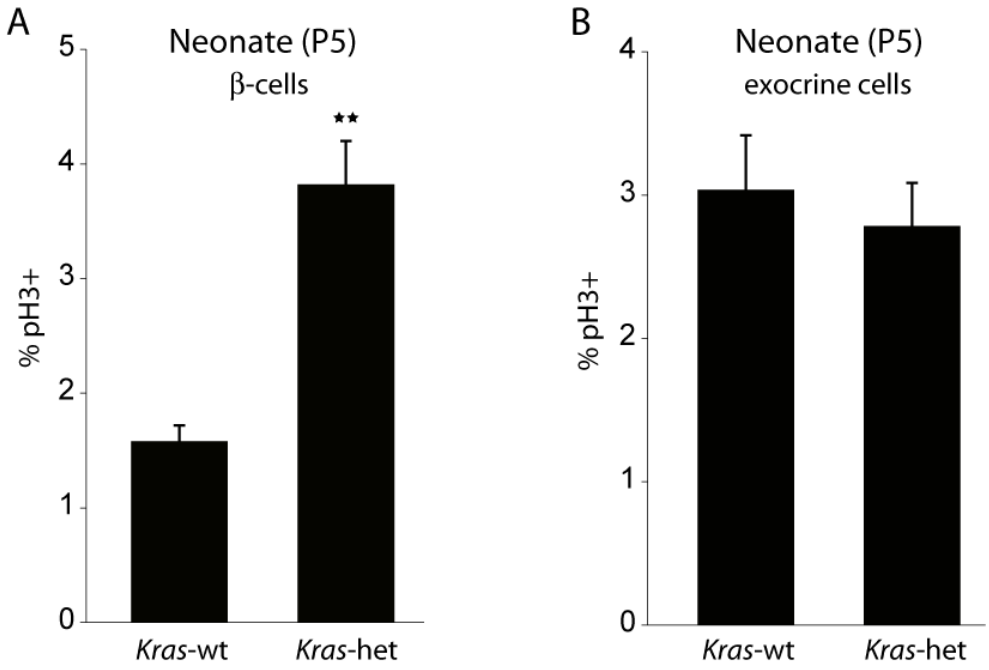

**Supplemental Figure 3**

Blood glucose levels were assayed in 10 week old *Kras*-het mice and wildtype littermates after intraperitoneal glucose injection (n=7 *Kras*-wt, n=5 *Kras*-het).



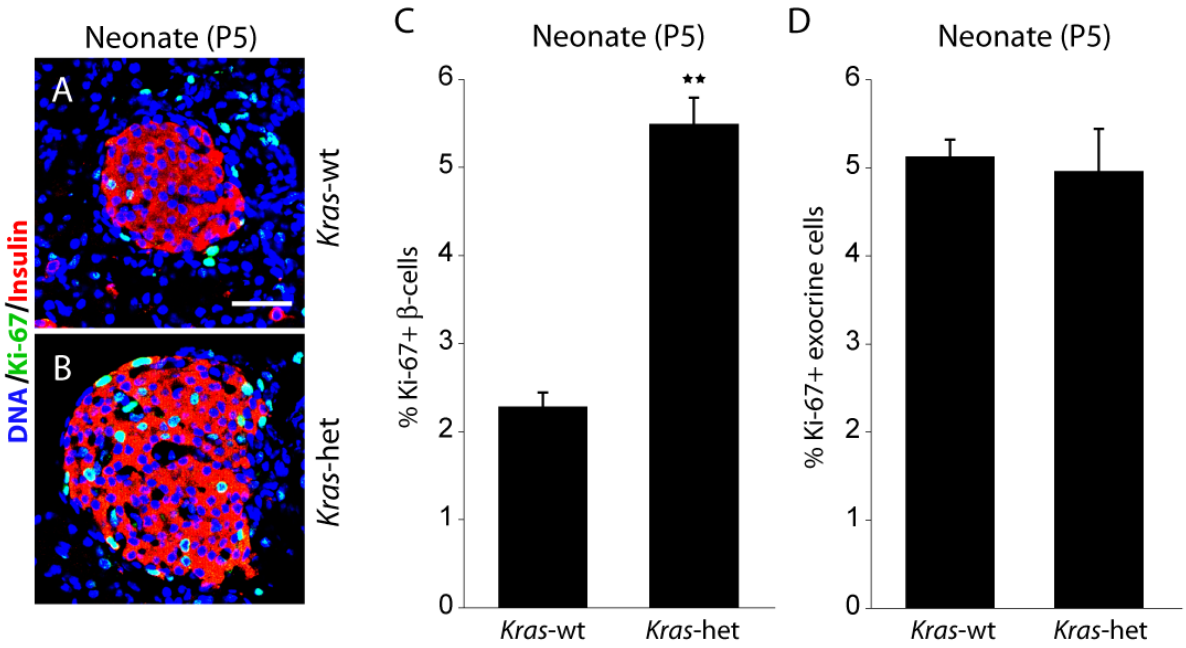

**Supplemental Figure 4**

Neurog3 expression domain in the developing mouse pancreas. (**A, B**) Projection images of the dorsal pancreas were collected by wholemount confocal microscopy from E13.5 mouse embryos with the indicated genotypes immunostained for E-Cadherin (blue) and Neurog3 (green). Scale bar is 50 μm.



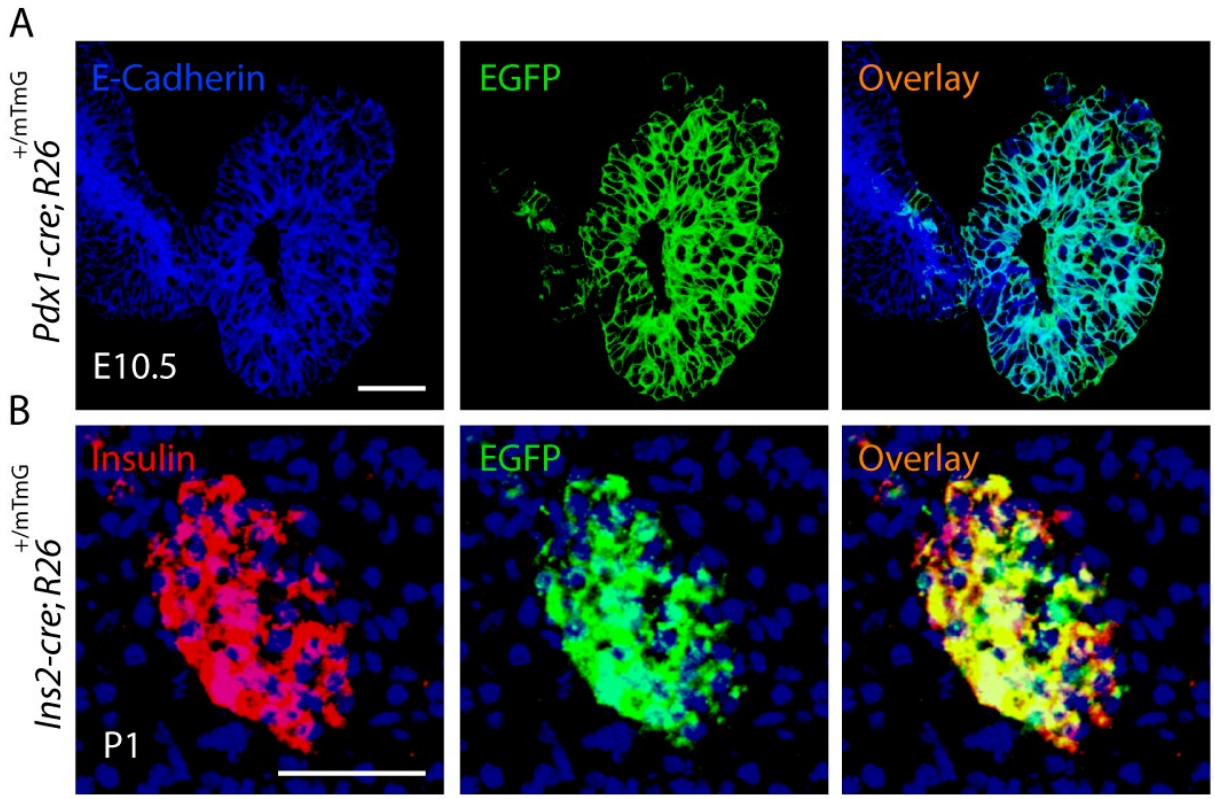

**Supplemental Figure 5**

β-cell proliferation in the pancreas of mouse neonates using pH3. Percentage of β-cells and exocrine cells expressing the proliferation marker pH3 was quantified in pancreases from P5 neonatal mice with the indicated genotypes (n=6 *Kras*-wt, n=6 *Kras*-het). All data points represent the mean ± SEM. **$p < 0.01$ vs. control by two-tailed Student's t test.



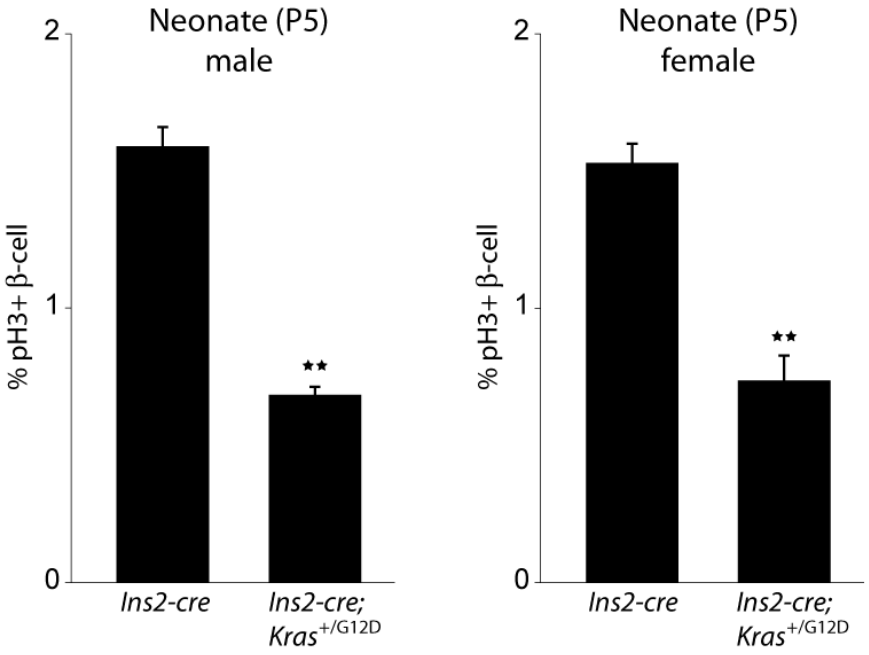

**Supplemental Figure 6**

β-cell proliferation in the pancreas of mouse neonates using Ki-67. Pancreatic sections from P5 wildtype (**A**) and *Kras*-het (**B**) neonates were immunostained for Insulin (red), the proliferation marker pH3 (green) and nuclear DNA with DAPI (blue). (**C, D**) Percentage of β-cells and exocrine cells expressing the proliferation marker Ki-67 was quantified in pancreases from P5 neonatal mice with the indicated genotypes (n=3 *Kras*-wt, n=3 *Kras*-het, >10000 β-cells and >29000 exocrine cells counted total). All data points represent the mean ± SEM. **$p < 0.01$ vs. control by two-tailed Student's t test. Scale bars are 50 μm.



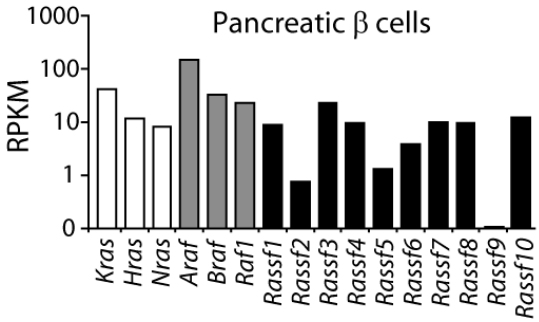

**Supplemental Figure 7**

Recombination efficiency of Cre transgenes. (**A, B**) Sagittal section of the dorsal pancreas from an E10.5 *Pdx1-cre*;*R26*$^{+/mTmG}$ mouse embryo immunostained for E-Cadherin (blue) and GFP (green) (**A**) and a section of the pancreas from a P1 *Ins2-cre*;*R26*$^{+/mTmG}$ mouse neonate immunostained for Insulin (red), GFP (green) and Topro3 (blue) (**B**). *R26*$^{+/mTmG}$ is a ROSA reporter allele that expresses membrane-targeted tandem dimer Tomato (mT) prior to Cre-mediated excision and membrane-targeted green fluorescent protein (mG) after excision (1). Note that *Pdx1-cre* and *Ins2-cre* drive efficient recombination throughout the embryonic pancreas and neonatal beta-cell population, respectively. Scale bars are 50 μm.



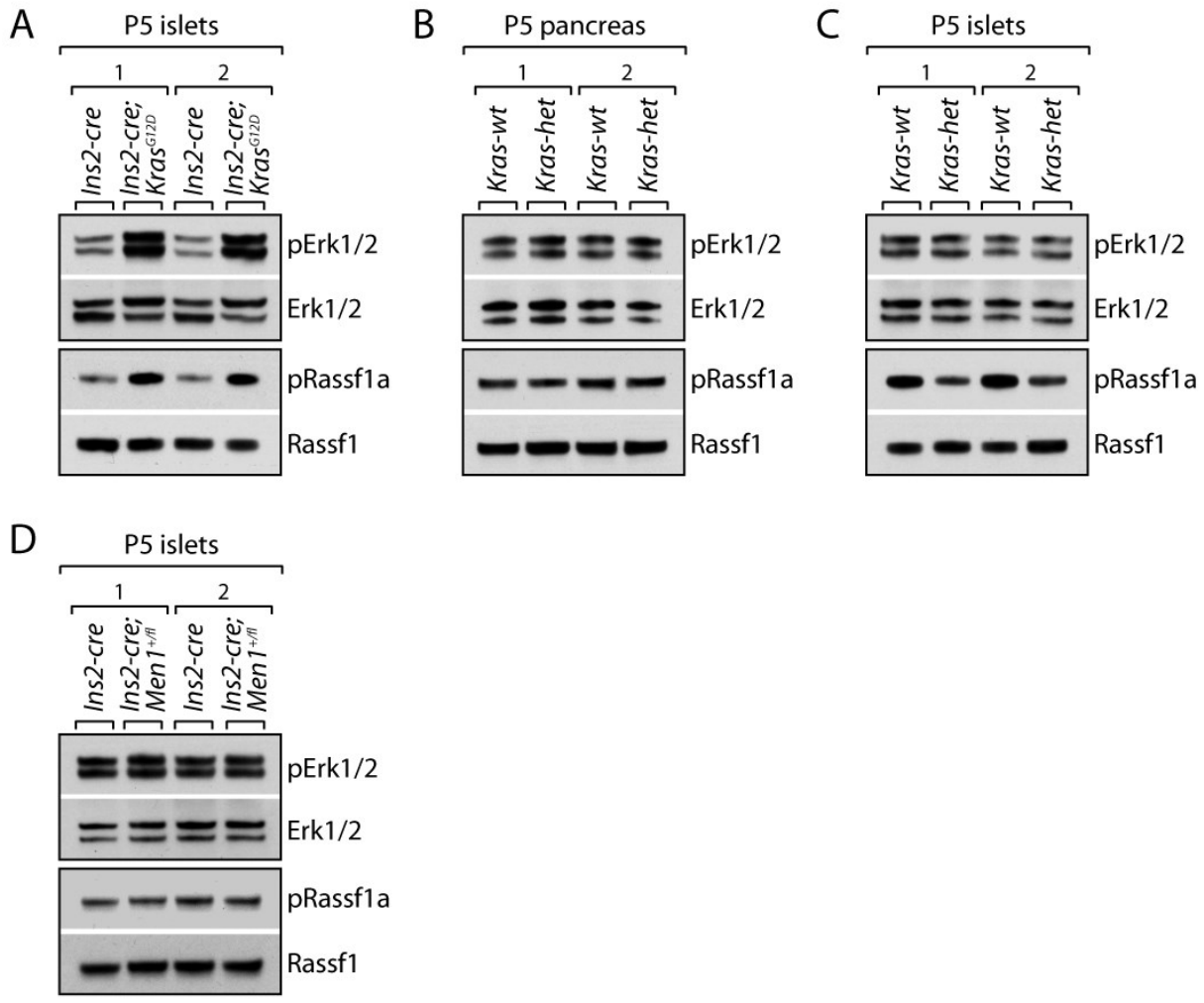

**Supplemental Figure 8**

β-cell proliferation in the pancreas of male and female mouse neonates. Percentage of β-cells expressing the proliferation marker pH3 was quantified in pancreases from P5 neonatal male and female mice with the indicated genotypes. Gender of pancreas samples was determined by PCR for the male specific *Sry* gene (2) (male: n=5 *Ins2-cre*, n=4 *Ins2-cre*;*Kras*$^{+/G12D}$; female: (n=4 *Ins2-cre*, n=5 *Ins2-cre*;*Kras*$^{+/G12D}$). All data points represent the mean ± SEM. **$p < 0.01$ vs. control by two-tailed Student's t test.



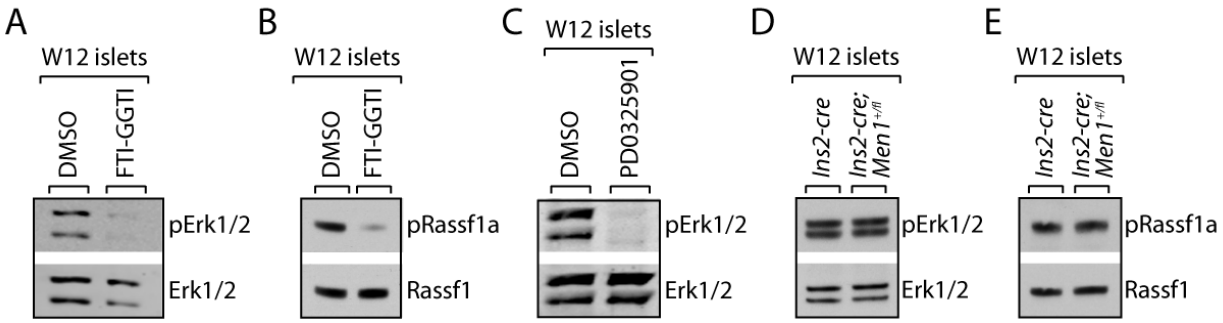

**Supplemental Figure 9**

Expression levels of members of Ras and Ras-effector families in adult mouse β-cells as determined by mRNA sequencing and expressed in reads per kilobase of exon model per million mapped reads (RPKM) (3).



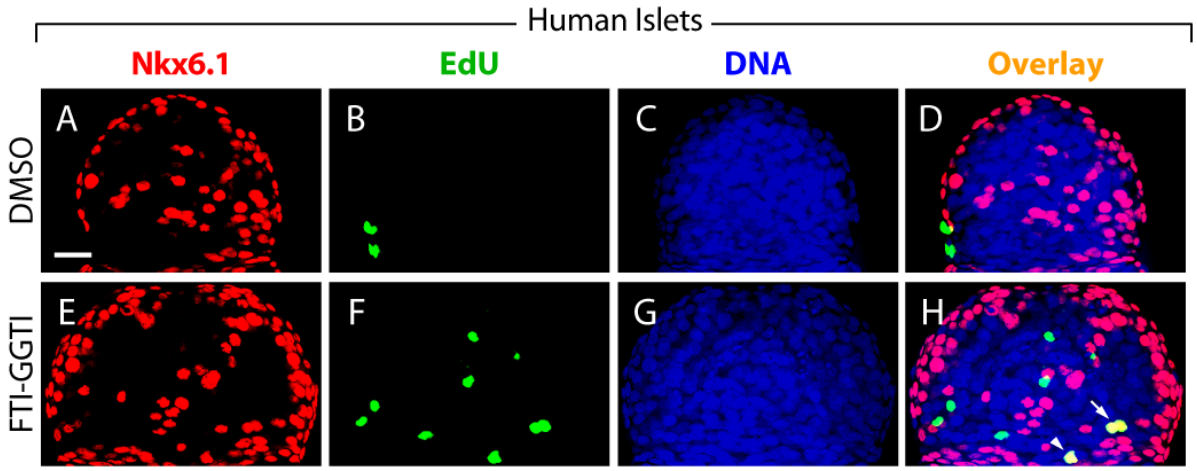

**Supplemental Figure 10**

(**A-C**) Western analysis of Erk1/2, phosphorylated-Erk1/2 (Thr202/Tyr204) (pErk1/2), Rassf1 and phosphorylated-Rassf1a (Ser131) (pRassf1a) using lysates from isolated mouse pancreases or islets (P5 neonates) of indicated genotypes. Two biological replicates represented for each.



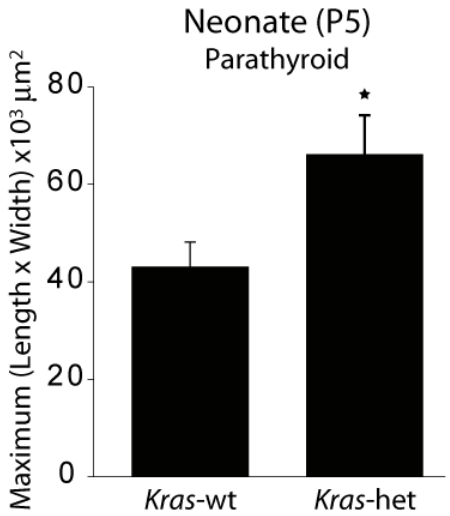

**Supplemental Figure 11**

Western analysis of pErk1/2, pErk1/2, Rassf1, pRassf1a in isolated mouse islets (from 12-week old males) of indicated treatments or genotypes.



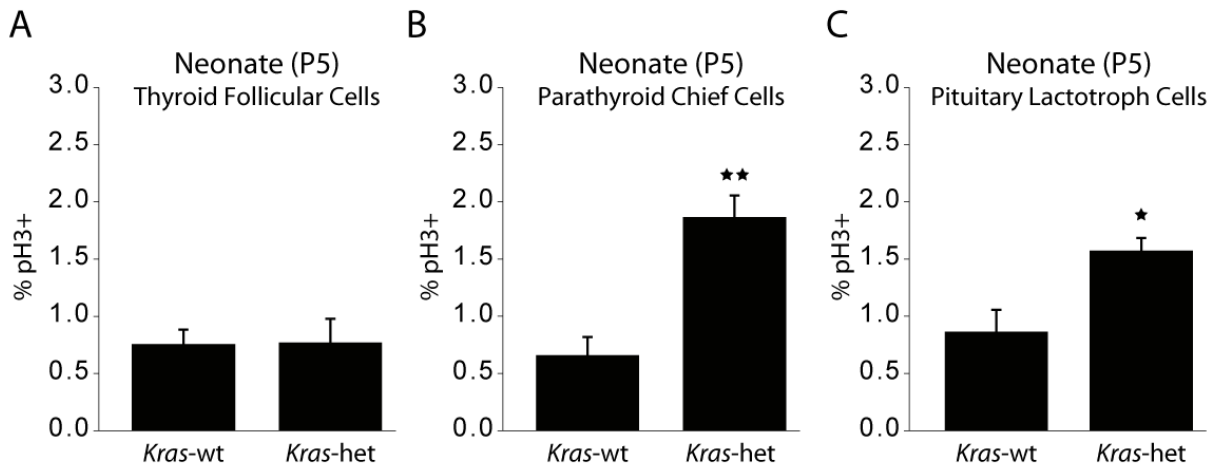

**Supplemental Figure 12**

β-cell proliferation in human islets. (**A-H**) Optical section images from wholemount confocal microscopy of cultured human pancreatic islets immunostained for β-cell marker Nkx6.1 (red), proliferation marker EdU (green) and nuclear DNA marker DAPI (blue). Treatments are indicated. EdU+/Nkx6.1+ co-positive β cells were not detected (nd) in control islets while EdU+/Nkx6.1 co-positive singlet (arrowhead) and doublet (arrow) β-cells were found in FTI-GGTI treated islets (72% singlet, 28% doublet). Donor was a 22-year old male.



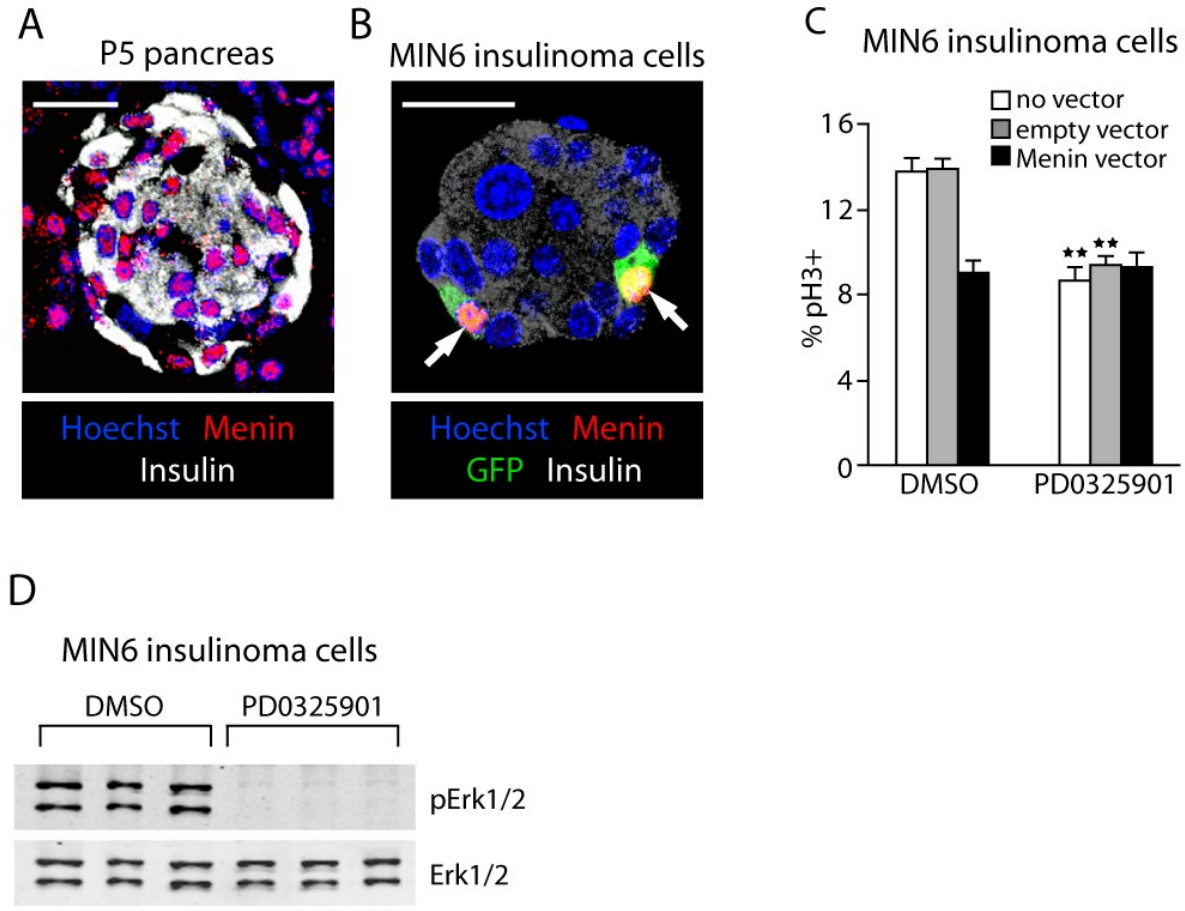

**Supplemental Figure 13**

Parathyroid size. Product of maximum length and width from cross-sections immunostained for Chromogranin A and DAPI (n=6 *Kras*-wt, n=6 *Kras*-het). All data points represent the mean ± SEM. *$p < 0.05$ vs. control or for the comparisons indicated by two-tailed Student's t test.




**Supplemental Figure 14**

Proliferation of MEN1-sensitive endocrine cell-types. Percentage of thyroid follicular cells (**A**), parathyroid chief cells (**B**) and pituitary lactotroph cells (**C**) expressing the proliferation marker pH3 was quantified in pancreases from P5 neonatal mice with the indicated genotypes . All data points represent the mean ± SEM (n=6 *Kras*-wt, n=6 *Kras*-het). *p<0.05, **p < 0.01 vs. control by two-tailed Student's t test.




**Supplemental Figure 15**

Effect of Menin expression on proliferation of MIN6 insulinoma cells. (**A, B**) Confocal image of the P5 mouse neonatal pancreas (**A**) and MIN6 insulinoma cells transfected with plasmid pMenin+iresGFP (see Methods), immunostained for Insulin (white), Menin (red), GFP (green) and Hoechst (blue). Note that Menin was not detected in non-transfected MIN6 cells. (**C**) Percentage of pH3 expressing MIN6 insulinoma cells transfected with the pMenin+iresGFP plasmid vector cultured with 10μM PD0325901 or vehicle control (DMSO). Transfected MIN6 cells were identified by the expression of green fluorescent protein (GFP). (**D**) Western analysis

of Erk1/2 and phosphorylated-Erk1/2 (pErk1/2) un-transfect MIN6 cells with DMSO or 10μM PD0325901. Scale bar is 25 μm.

**Supplemental References**


1. Muzumdar, M.D., Tasic, B., Miyamichi, K., Li, L., and Luo, L. 2007. A global double-fluorescent Cre reporter mouse. *Genesis* 45:593-605.
2. Lavrovsky, Y., Song, C.S., Chatterjee, B., and Roy, A.K. 1998. A rapid and reliable PCR-based assay for gene transmission and sex determination in newborn transgenic mice. *Transgenic Res* 7:319-320.
3. Ku, G.M., Kim, H., Vaughn, I.W., Hangauer, M.J., Oh, C.M., German, M.S., and McManus, M.T. 2012. Research Resource: RNA-Seq Reveals Unique Features of the Pancreatic beta-Cell Transcriptome. *Mol Endocrinol*.