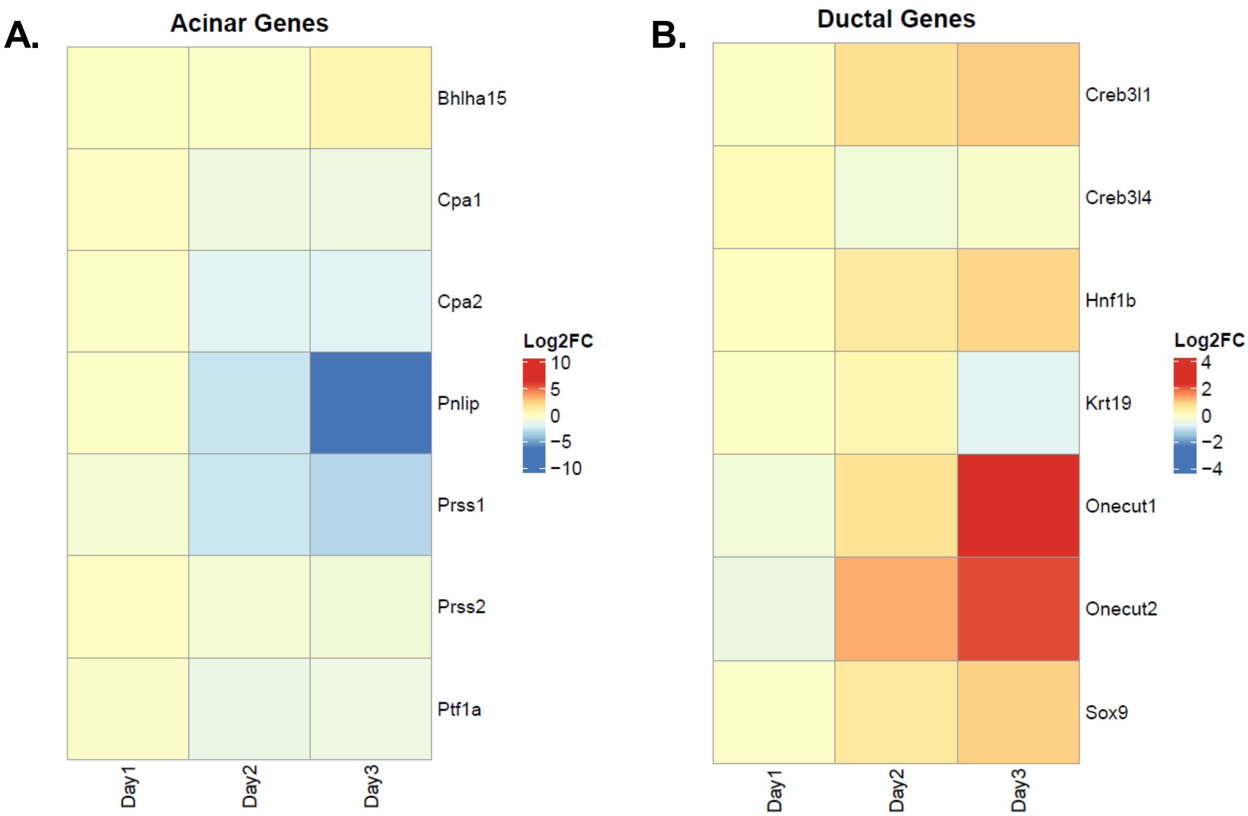
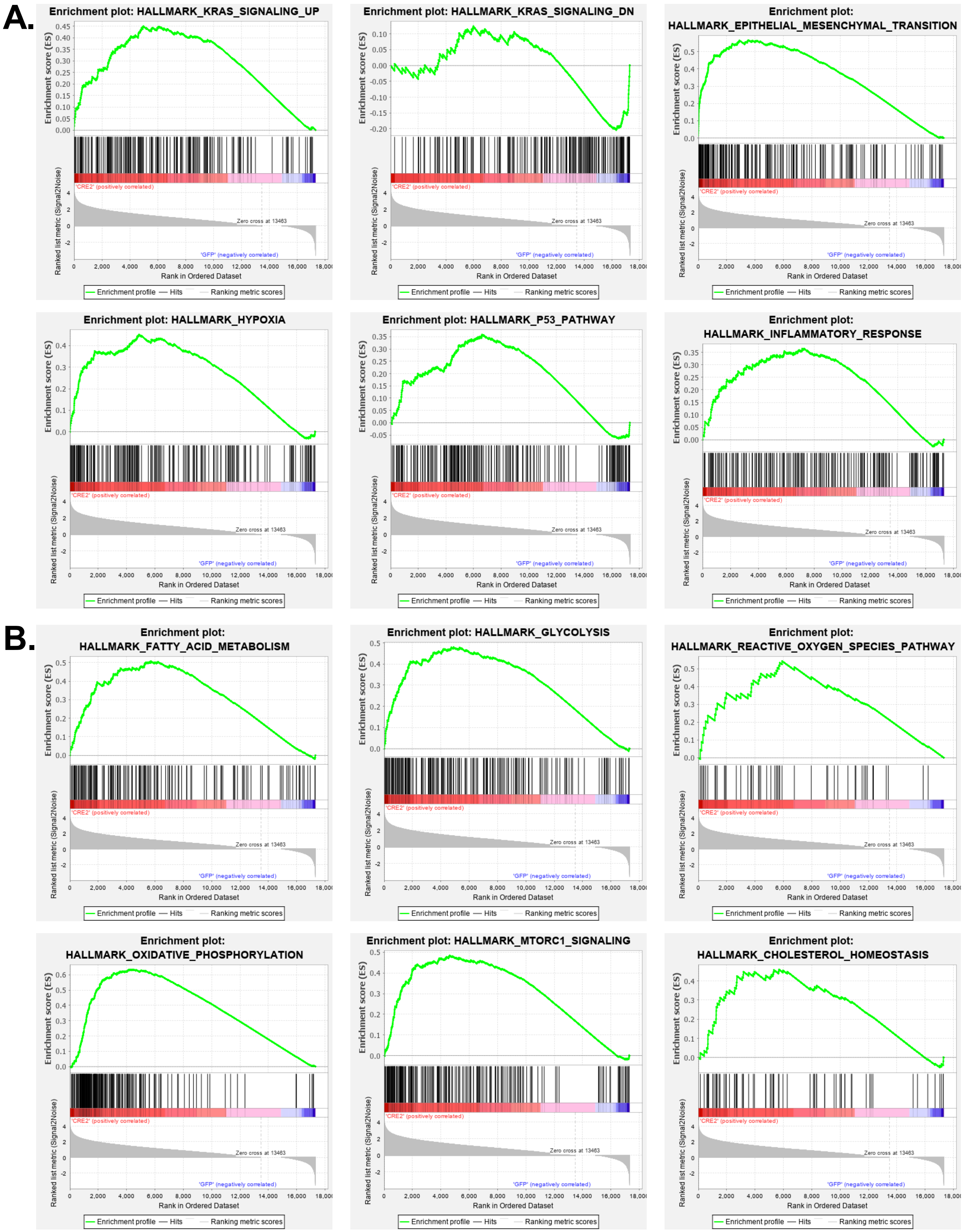

A.
Acinar Genes
Bhlha15
Cpa1
Cpa2
Pnlip
Prss1
Prss2
Ptf1a
Day1
Day2
Day3
Log2FC
10
5
0
−5
−10
B.
Ductal Genes
Creb3l1
Creb3l4
Hnf1b
Krt19
Onecut1
Onecut2
Sox9
Day1
Day2
Day3
Log2FC
4
2
0
−2
−4

Supplemental Figure 1. Heatmaps of acinar and ductal genes from RNA-sequencing

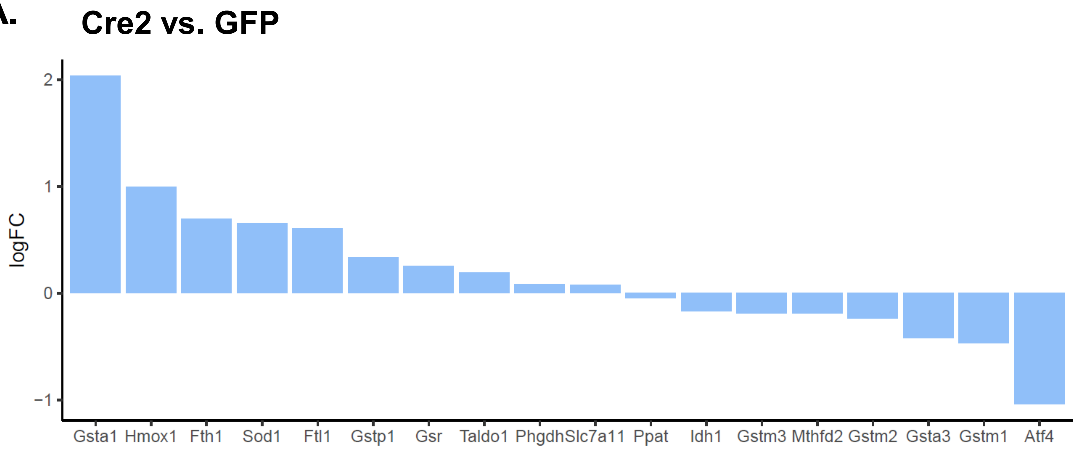
A. Log_2FC expression of several acinar genes from RNA-sequencing of *ex vivo* acinar cell cultures at Day 1, 2, or 3 compared to GFP.

B. Log_2FC expression of several ductal/ADM genes from RNA-sequencing of *ex vivo* acinar cell cultures at Day 1, 2, or 3 compared to GFP.

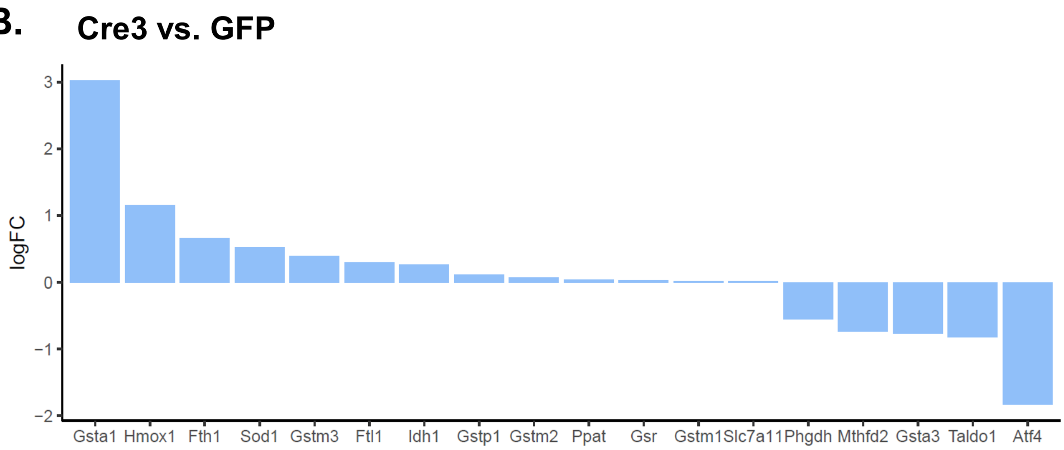

A.
Enrichment plot: HALLMARK_KRAS_SIGNALING_UP
Enrichment plot: HALLMARK_KRAS_SIGNALING_DN
Enrichment plot: HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION
Enrichment plot: HALLMARK_HYPOXIA
Enrichment plot: HALLMARK_P53_PATHWAY
Enrichment plot: HALLMARK_INFLAMMATORY_RESPONSE
B.
Enrichment plot: HALLMARK_FATTY_ACID_METABOLISM
Enrichment plot: HALLMARK_GLYCOLYSIS
Enrichment plot: HALLMARK_REACTIVE_OXYGEN_SPECIES_PATHWAY
Enrichment plot: HALLMARK_OXIDATIVE_PHOSPHORYLATION
Enrichment plot: HALLMARK_MTORC1_SIGNALING
Enrichment plot: HALLMARK_CHOLESTEROL_HOMEOSTASIS
Enrichment score (ES)
Ranked list metric (Signal2Noise)
'CRE2' (positively correlated)
Zero cross at 13463
'GFP' (negatively correlated)
Rank in Ordered Dataset
Enrichment profile
Hits
Ranking metric scores

Supplemental Figure 2. Differentially expressed pathways and GSEAs from RNA-sequencing
A. Selected Hallmark GSEA plots of known pathways in ADM that are enriched in *Kras*^{G12D}-expressing acinar cells (Cre2 vs. GFP).
B. Selected Hallmark GSEA plots of metabolic pathways that are enriched in *Kras*^{G12D}-expressing acinar cells (Cre2 vs. GFP).
Enrichment score (ES) signifies the degree a gene set is overrepresented at the top or bottom of a ranked list of genes. The black vertical bars show where genes within the gene set appear in ranked list. The waterfall plot represents a gene's correlation with a phenotype.

A.


Cre2 vs. GFP
logFC
2
1
0
−1
Gsta1 Hmox1 Fth1 Sod1 Ftl1 Gstp1 Gsr Taldo1 Phgdh Slc7a11 Ppat Idh1 Gstm3 Mthfd2 Gstm2 Gsta3 Gstm1 Atf4

B.


Cre3 vs. GFP
logFC
3
2
1
0
−1
−2
Gsta1 Hmox1 Fth1 Sod1 Gstm3 Ftl1 Idh1 Gstp1 Gstm2 Ppat Gsr Gstm1 Slc7a11 Phgdh Mthfd2 Gsta3 Taldo1 Atf4

Supplemental Figure 3. Additional NRF2 target genes from RNA-sequencing
A. LogFC expression of additional NRF2-target genes from RNA-sequencing of *Kras*^{G12D}-expressing acinar cells when comparing Cre2 to GFP.
B. LogFC expression of additional NRF2-target genes from RNA-sequencing of *Kras*^{G12D}-expressing acinar cells when comparing Cre3 to GFP.

♀ Ptf1a$^{Cre/+}$;G6pd$^{mut/wt}$

X

♂ LSL-Kras^{G12D};G6pd$^{mut/y}$

or

♂ LSL-Kras^{G12D};G6pd$^{wt/y}$

<u>Mutant:</u>

♀ LSL-Kras^{G12D}; Ptf1a$^{Cre/+}$;G6pd$^{mut/mut}$

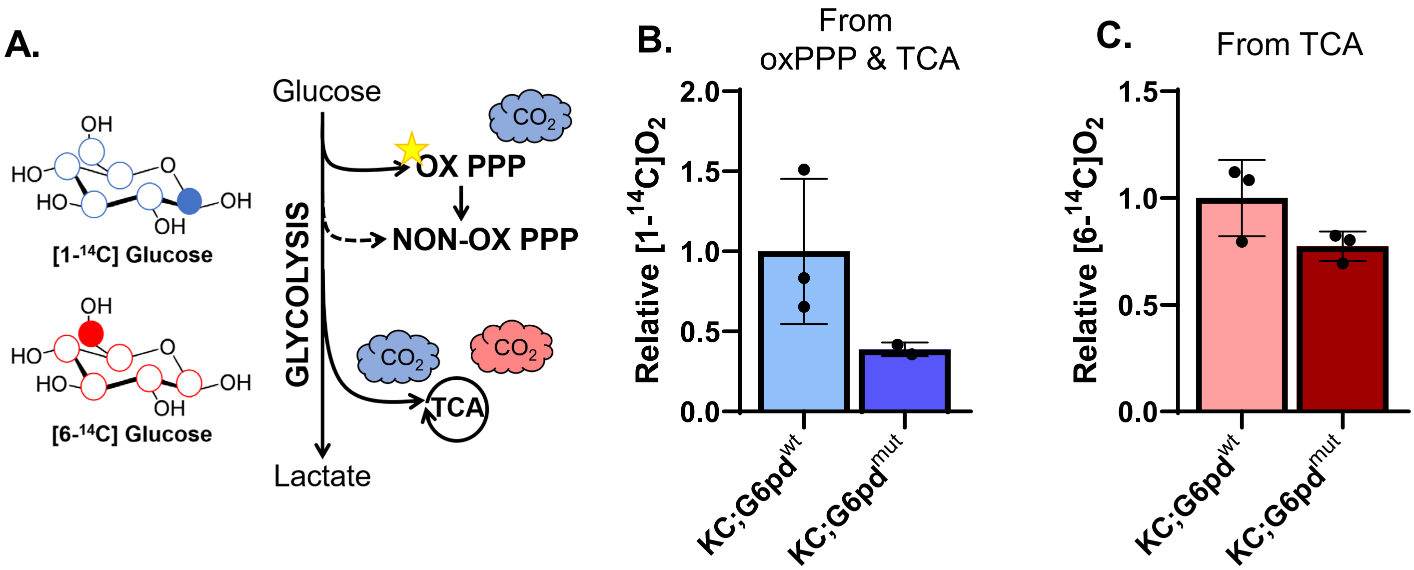
♂ LSL-Kras^{G12D}; Ptf1a$^{Cre/+}$ G6pd$^{mut/y}$

<u>Wildtype:</u>

♀ LSL-Kras^{G12D}; Ptf1a$^{Cre/+}$;G6pd$^{wt/wt}$

♂ LSL-Kras^{G12D}; Ptf1a$^{Cre/+}$;G6pd$^{wt/y}$

Supplemental Figure 4. Breeding scheme to generate KC;G6pd^{mut} and KC;G6pd^{wt} mice
Mice with mutant *G6pd*, that mimics human G6PD-deficiency, were bred into the KC (*LSL-Kras$^{G12D/+}$; Ptf1aCre*) line. *Ptf1aCre* was always maintained in female breeders. Experiments used both male and female *G6pd* mutant mice, where females were homozygous for mutant *G6pd* (*G6pd$^{mut/mut}$*) and males were hemizygous for mutant *G6pd* (*G6pd$^{mut/y}$*), as *G6pd* is an X-linked gene. *G6pd* wildtype mice used in experiments were obtained in the same colony and age matched littermates of *G6pd* mutant mice when possible. Female *G6pd* wildtype mice have two wildtype copies of *G6pd* (*G6pd$^{wt/wt}$*) and males have one wildtype copy (their only copy) of *G6pd* (*G6pd$^{wt/y}$*). In the schematics and labelling, "y" in male mice refers to the y chromosome, which does not contain a copy of *G6pd*.


A.
OH
HO
O
HO
OH
OH
[1-14C] Glucose
OH
HO
O
HO
OH
OH
[6-14C] Glucose
Glucose
CO2
OX PPP
NON-OX PPP
GLYCOLYSIS
CO2
CO2
TCA
Lactate
B.
From
oxPPP & TCA
2.0
1.5
1.0
0.5
0.0
Relative [1-14C]O2
KC;G6pd^wt
KC;G6pd^mut
C.
From TCA
1.5
1.0
0.5
0.0
Relative [6-14C]O2
KC;G6pd^wt
KC;G6pd^mut

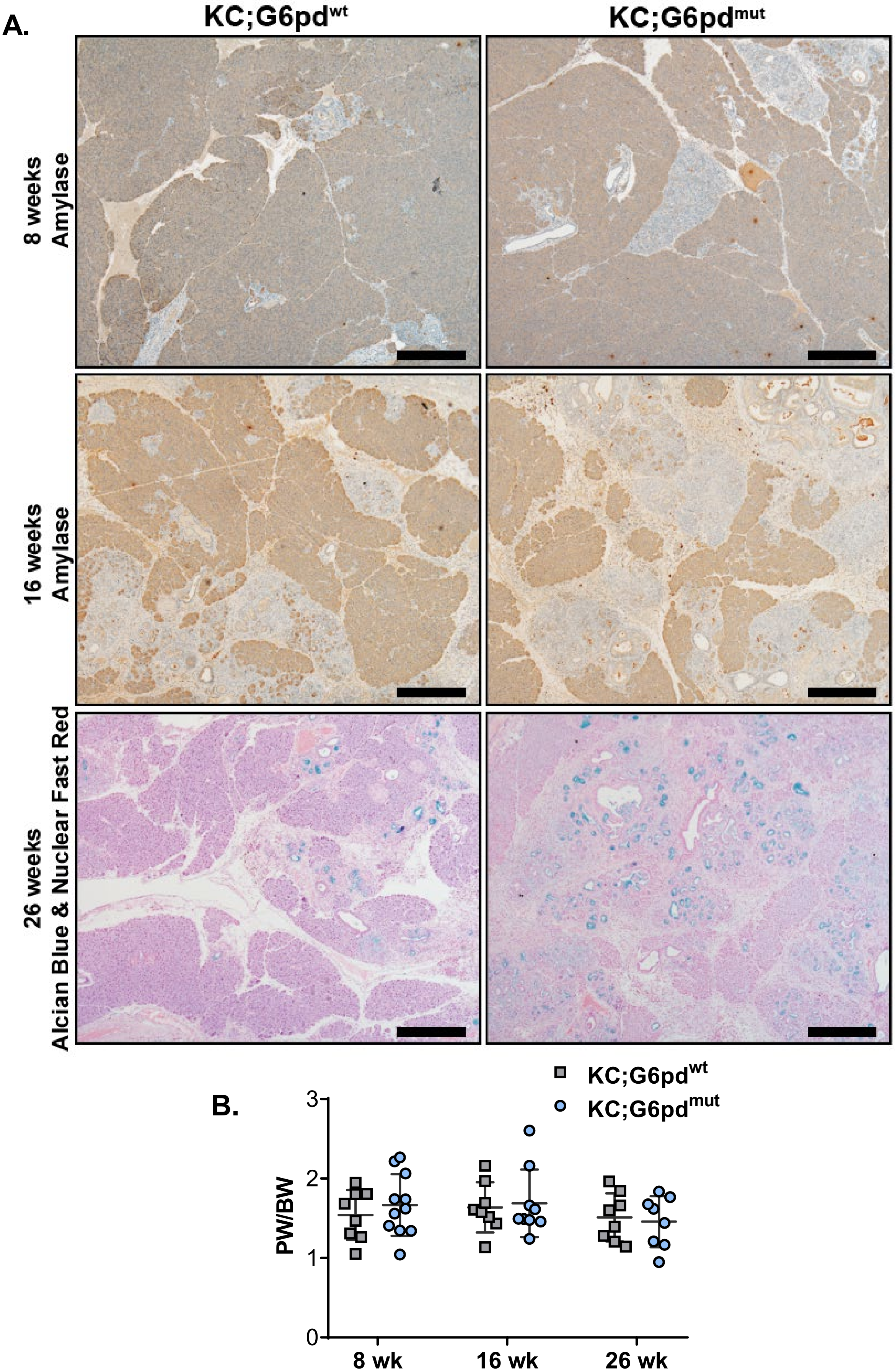
Supplemental Figure 5. ^{14}C-labeling in acinar cells

A. Schematic of ^{14}C-labeling experiment. [1-^{14}C]glucose (blue) can be used in both the oxidative pentose phosphate pathway (ox PPP) and the TCA cycle. [6-^{14}C]glucose (red) can be used in the TCA cycle.

B. Relative amount of [^{14}C]-labeled CO_2 derived from [1-^{14}C]glucose. [1-^{14}C]O_2 is generated from either the oxidative pentose phosphate pathway or the TCA cycle.

C. Relative amount of [^{14}C]-labeled CO_2 derived from [6-^{14}C]glucose. [6-^{14}C]O_2 is only generated from the TCA cycle.

Each point in B and C represents technical replicates from one mouse.


A.
KC;G6pd^{wt}
KC;G6pd^{mut}
8 weeks Amylase
16 weeks Amylase
26 weeks Alcian Blue & Nuclear Fast Red
B.
KC;G6pd^{wt}
KC;G6pd^{mut}
PW/BW
0
1
2
3
8 wk
16 wk
26 wk

Supplemental Figure 6. Low magnification images of Amylase and Alcian blue in pancreata and pancreas weight to body weight ratios

A. Immunostaining for Amylase (AMY), in 8-week and 16-week-old KC;G6pd^{wt} and KC;G6pd^{mut} pancreas. Alcian blue (PanIN-produced mucin) & nuclear fast red counterstain in pancreas of 26-week-old KC;G6pd^{wt} and KC;G6pd^{mut} mice. Scale bar = 500μm.

B. Pancreas weight (PW) to body weight (BW) ratios in 8-, 16-, and 26-week-old KC;G6pd^{wt} and KC;G6pd^{mut} mice.