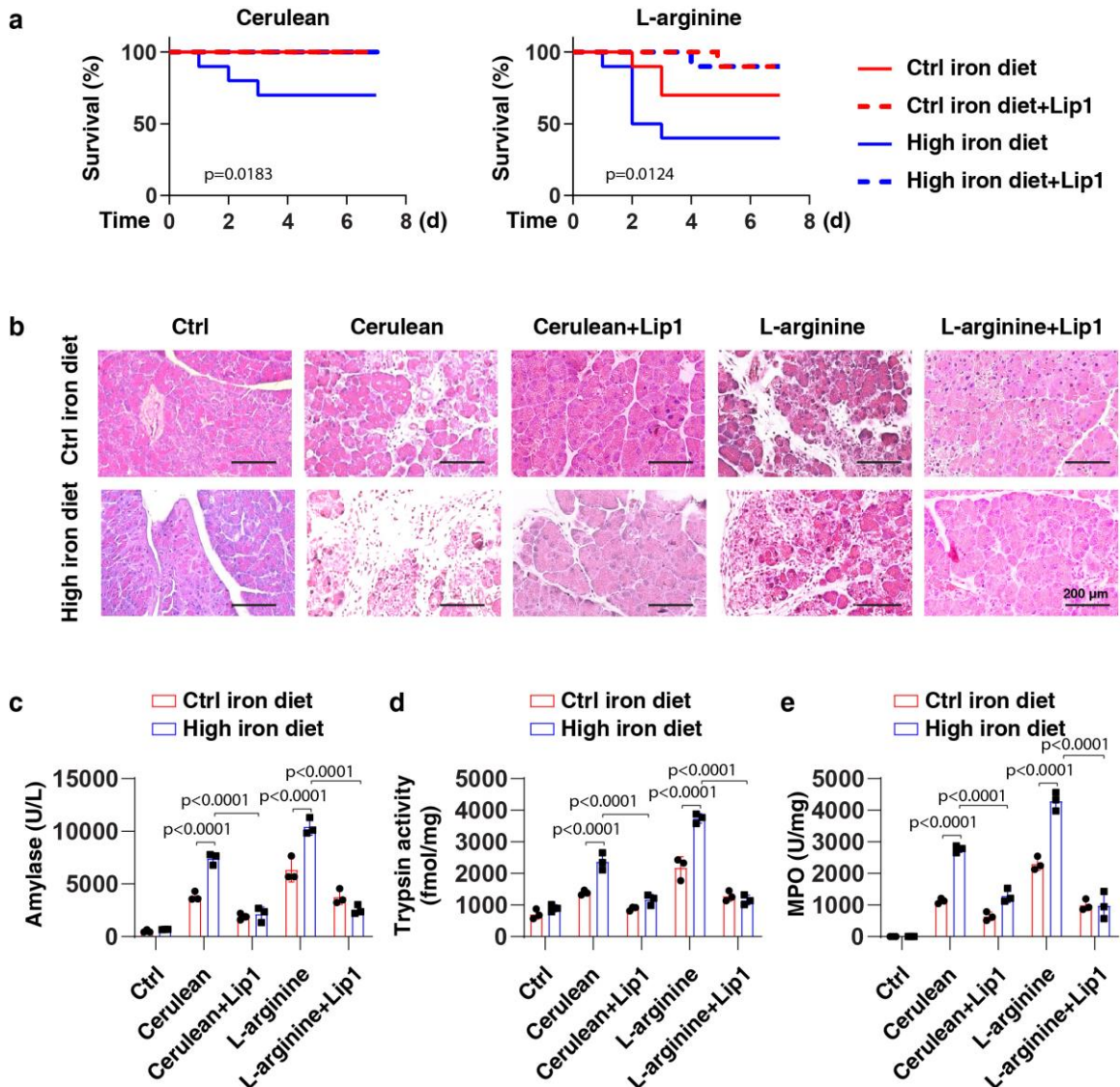
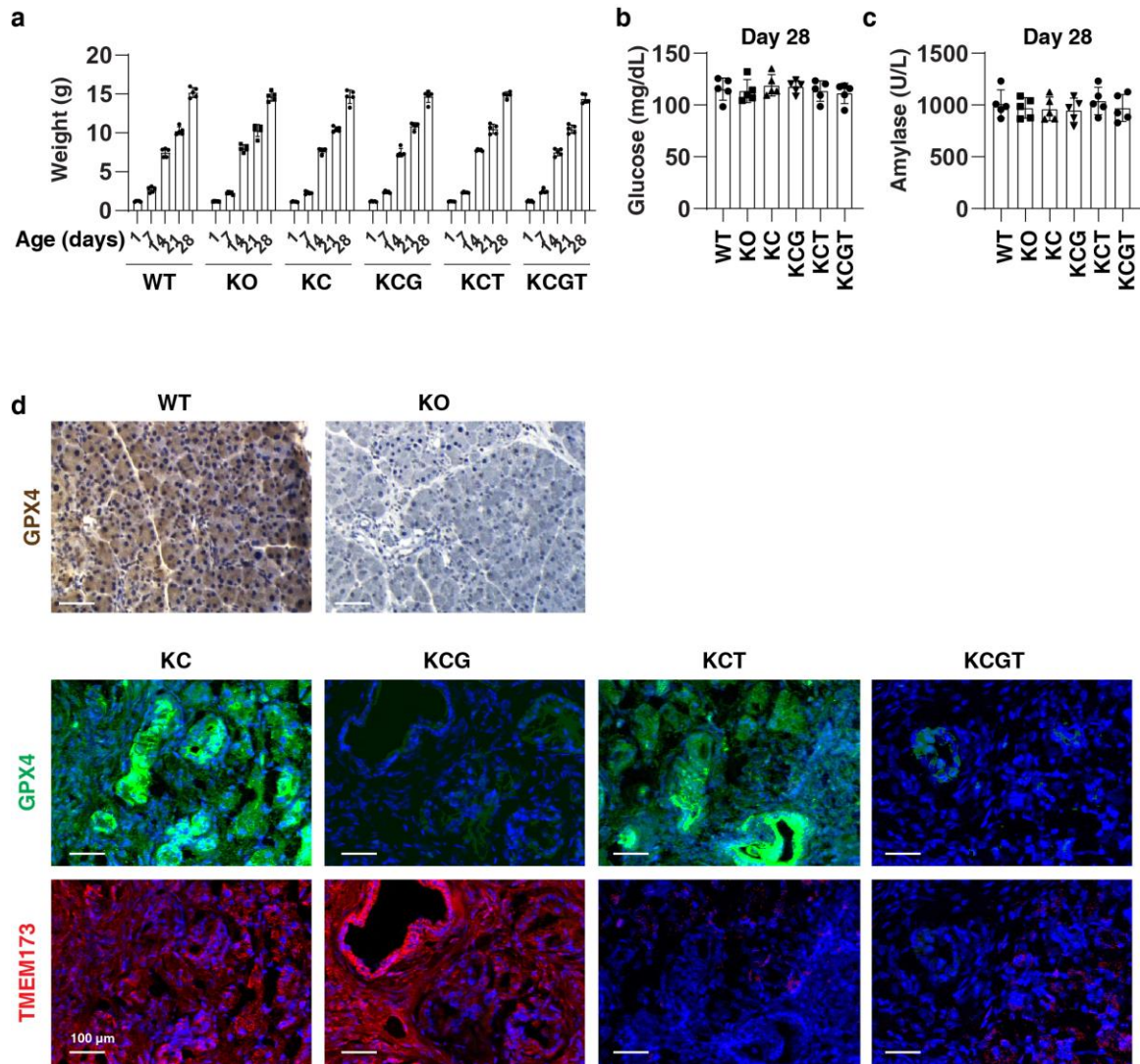


Supplementary Information

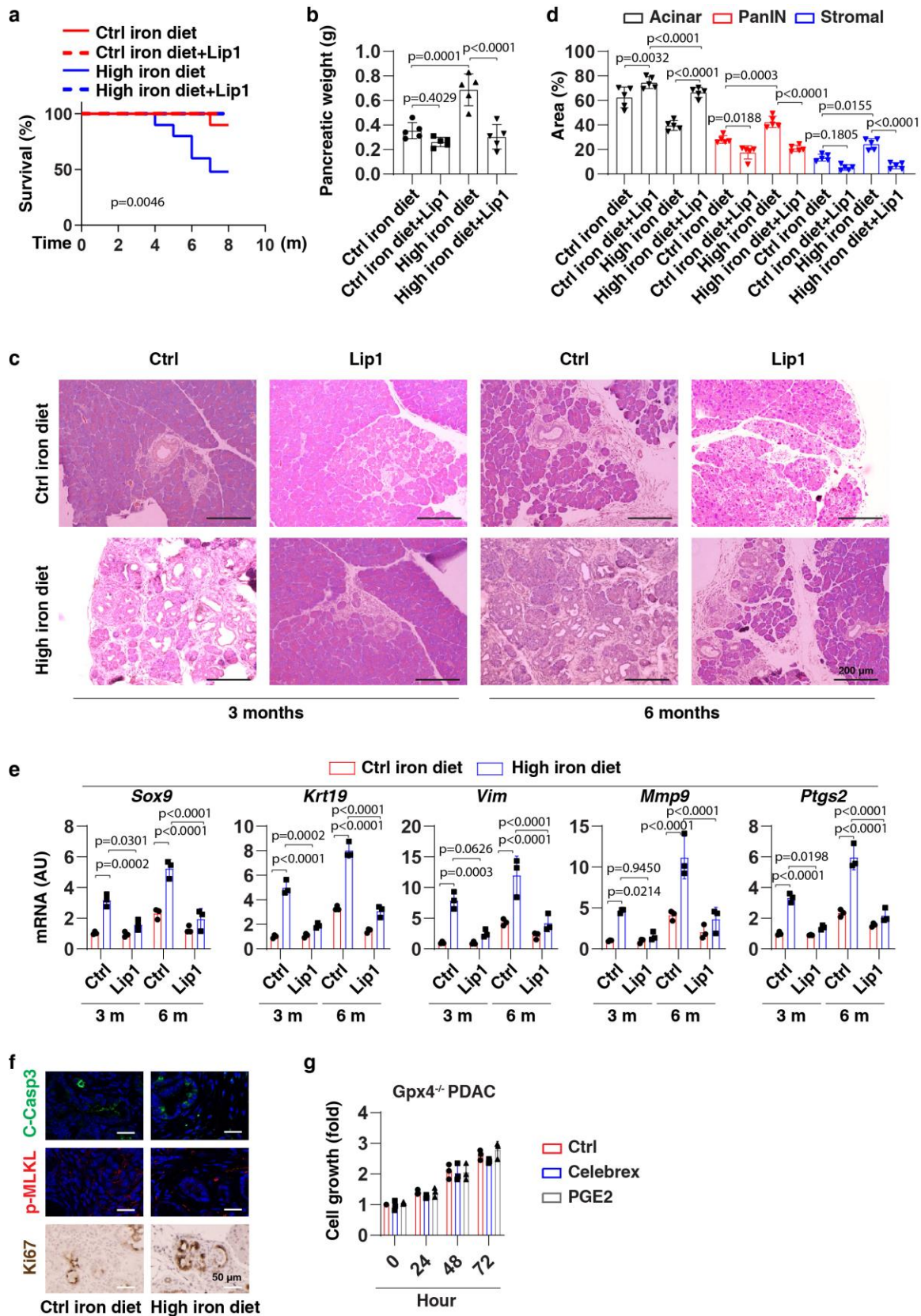


Supplementary Figure 1. A high-iron diet promotes experimental pancreatitis. (a) Survival of mice with control or high-iron diet in cerulean- or L-arginine-induced pancreatitis with or without liproxstatin-1 (Lip1) treatment (n = 10 mice/group; one-sided Log-rank [Mantel-Cox] test). (b-e) In parallel, pancreas histology (b), plasma amylase activity (c), pancreatic trypsin activity (d), and pancreatic myeloperoxidase (MPO) activity (e) at 24 hours were assayed (n = 3 mice/group; two way

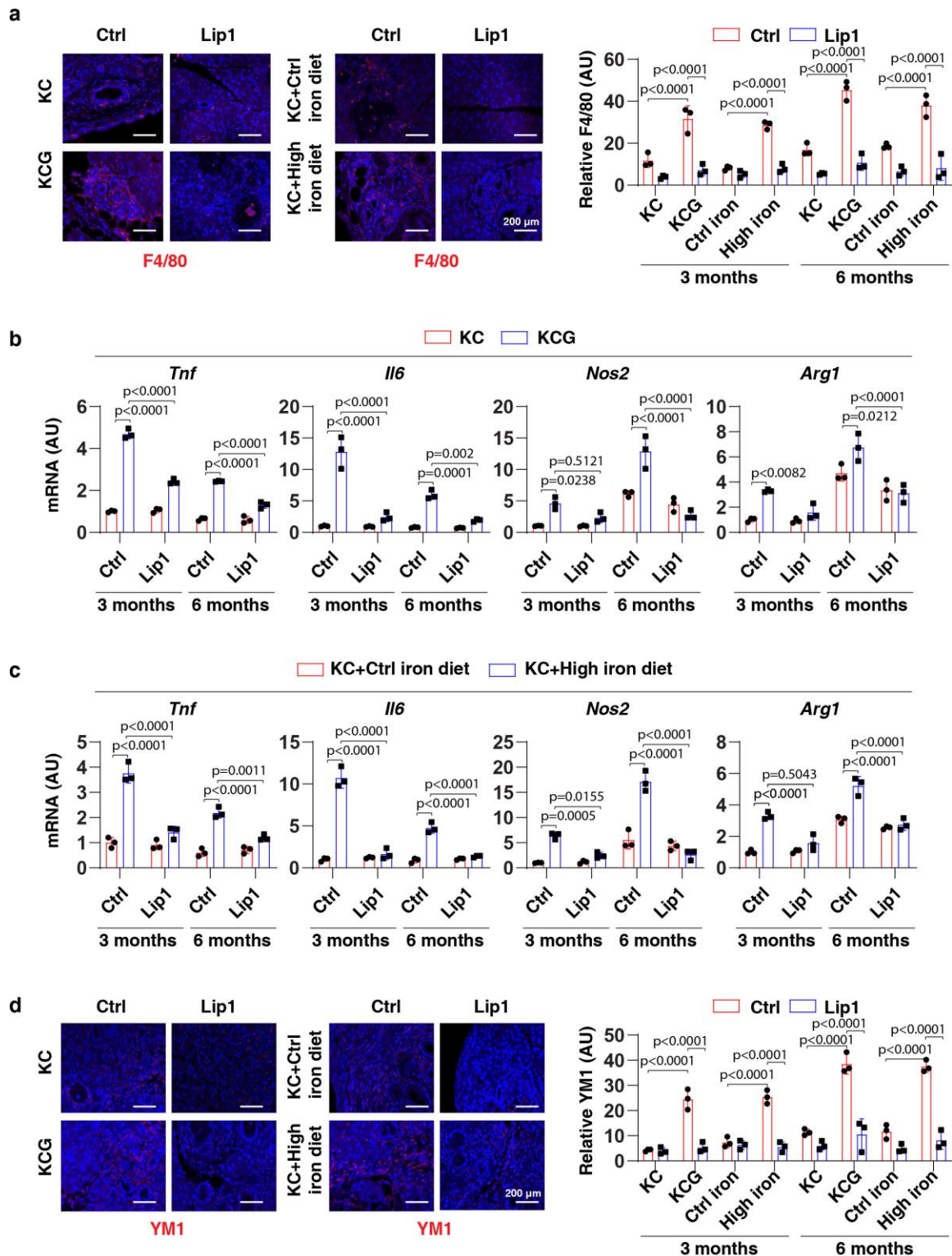
ANOVA with Tukey's multiple comparisons test). Data in (c-e) are presented as mean $\pm$ SD. Data are from two or three independent experiments.



Supplementary Figure 2. Effect of GPX4 and/or TMEM173 deletion on pancreatic function. (a-c) The weight, blood glucose, and blood amylase of indicated mice. (d) IHC or IF staining of GPX4 and TMEM173 on indicated mice at the age of 3 months. Data in (a-c) are presented as mean $\pm$ SD (n = 5 mice/group). Data are from two independent experiments.



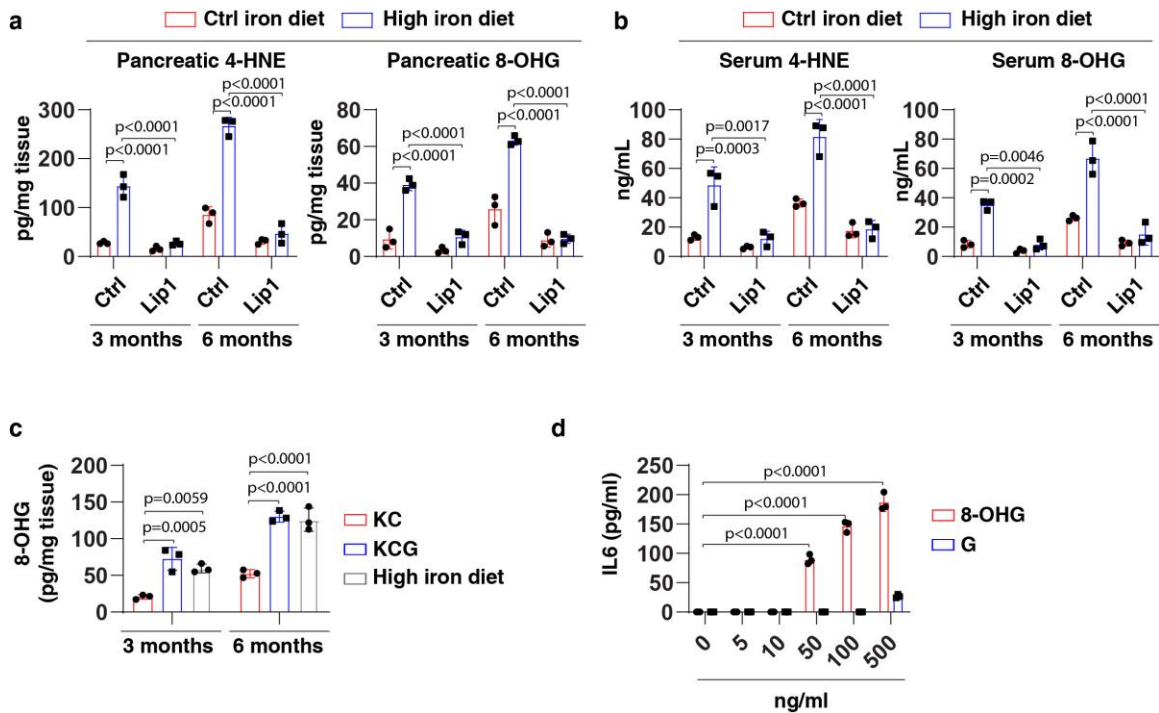
Supplementary Figure 3. A high-iron diet promotes *Kras*-driven pancreatic tumorigenesis. (a) Survival of *Pdx1-Cre;Kras^{G12D/+}* (KC) mice with control or high-iron diet with or without liproxstatin-1 (Lip1) treatment (n = 10 mice/group; one-sided Log-rank [Mantel-Cox] test). (b) Pancreas weight of the indicated mice (6 months; n = 5 mice/group; one way ANOVA with Tukey's multiple comparisons test). (c) Representative pancreas histology of the indicated mice. (d) Percentages of histological structures in the pancreas of the indicated mice (6 months; n = 5 mice/group; two way ANOVA with Tukey's multiple comparisons test). (e, f) Relative gene or protein expression in the pancreas of the indicated mice (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). (g) Cell growth in primary *Gpx4^{-/-}* PDAC cells in the absence or presence of celecoxib (50 nM) or PGE2 (5 ng/ml) for 24-72 hours. Data in (b, d, e, and g) are presented as mean $\pm$ SD. Data are from two or three independent experiments.



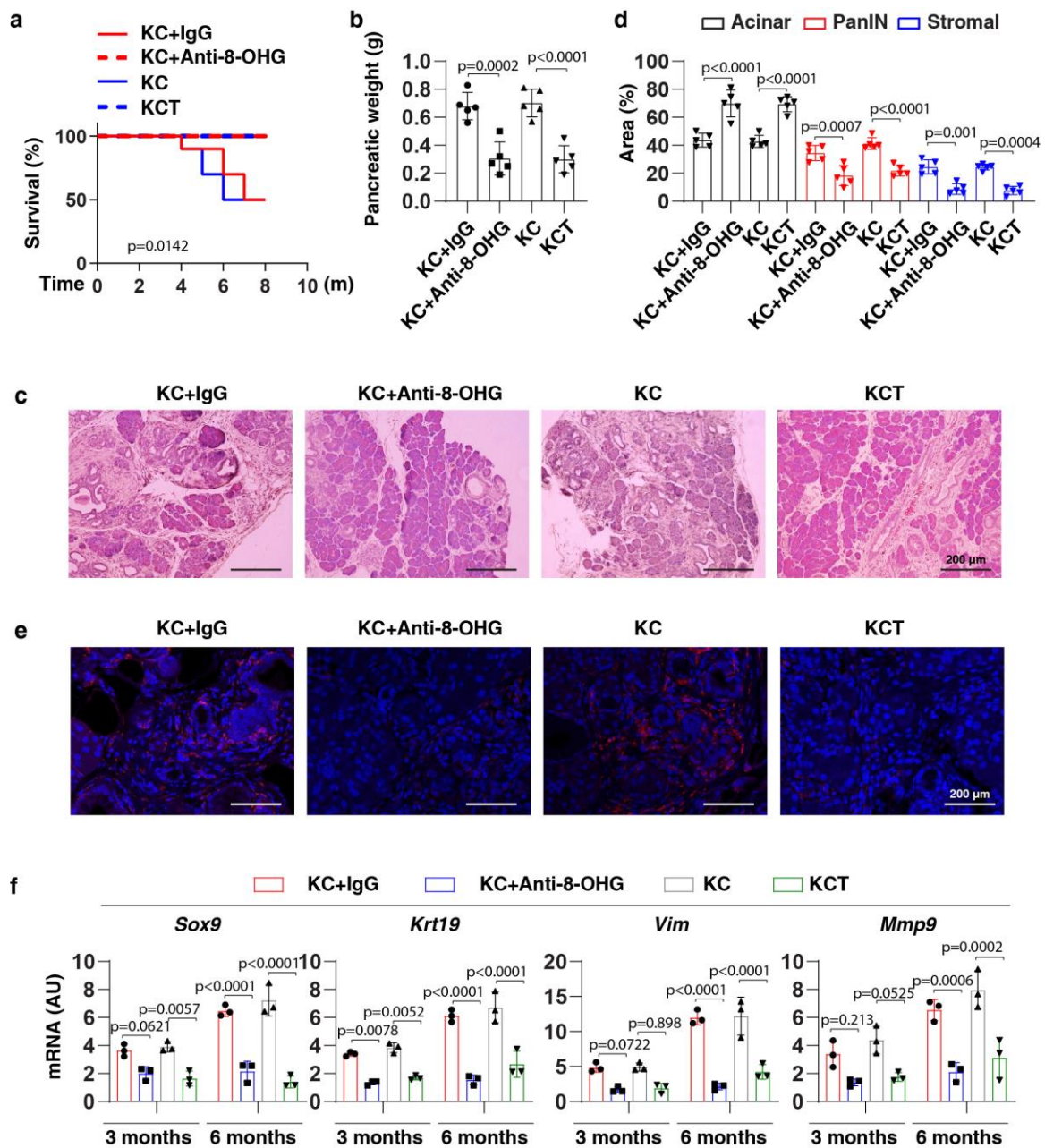
Supplementary Figure 4. *Gpx4* depletion or a high-iron diet promotes macrophage infiltration and activation during pancreatic tumorigenesis.

(a) Immunofluorescence staining of macrophages in pancreas by anti-F4/80 antibody

(red) in indicated mice at the age of 3 and 6 months (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). (b, c) Relative gene expression in tumor-associated macrophages in indicated mice (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). (d) Immunofluorescence staining of YM1 (red) in pancreas in indicated mice at the age of 3 and 6 months (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). Data in (a-d) are presented as mean $\pm$ SD. Data are from two or three independent experiments.



Supplementary Figure 5. A high-iron diet promotes 4-HNE and 8-OHG production and release. ELISA assay levels of 4-HNE or 8-OHG in the pancreas (a) or serum (b) in *Pdx1-Cre;Kras^{G12D/+}* (KC) mice with control or high-iron diet (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). (c) LC-MS/MS assay levels of 8-OHG in the pancreas in KC, KCG, or KC mice with high-iron diet (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). (d) Mouse bone marrow-derived macrophages (BMDMs) were treated with 8-OHG (5-500 ng/ml) or guanosine ("G", 5-500 ng/ml) for 24 hours. The release of IL6 were assayed (n = 3; two way ANOVA with Tukey's multiple comparisons test). Data in (a-d) are presented as mean $\pm$ SD. Data are from two independent experiments.



Supplementary Figure 6. TMEM173 facilitates pancreatic tumorigenesis.

(a) Survival of *Pdx1-Cre;Kras^{G12D/+}* (KC) or *Pdx1-Cre;Kras^{G12D/+};Tmem173^{-/-}* (KCT) mice with or without treatment of control IgG or anti-8-OHG antibody on high-iron diets (n =10 mice/group; one-sided Log-rank [Mantel-Cox] test). (b) Pancreas weight of the indicated mice (6 months; n = 5 mice/group; one way ANOVA with

Tukey's multiple comparisons test). (c) Representative pancreas histology of the indicated mice on high-iron diets. (d) Percentages of histological structures in the pancreas of the indicated mice at the age of 3 months on high-iron diets (n = 5 mice/group; two way ANOVA with Tukey's multiple comparisons test). (e) Representative images of immunofluorescence staining of macrophages (red) in pancreas of indicated mice at the age of 3 months on high-iron diets. (f) Relative gene expression in the pancreas of the indicated mice on high-iron diets (n = 3 mice/group; two way ANOVA with Tukey's multiple comparisons test). Data in (b, d, and f) are presented as mean $\pm$ SD. Data are from two or three independent experiments.

Supplementary Table 1

Primers used in this study

Gene	Forward	Reverse
mouse <i>Sox9</i>	5'-CACACGTCAAGCGACCCATGAA-3'	5'-TCTTCTCGCTCTCGTTCAGCAG-3'
mouse <i>Krt19</i>	5'-AATGGCGAGCTGGAGGTGAAGA-3'	5'-CTTGGAGTTGTCAATGGTGGCAC-3'
mouse <i>Vim</i>	5'-CGGAAAGTGGAATCCTTGCAGG-3'	5'-AGCAGTGAGGTCAGGCTTGGA-3'
mouse <i>Mmp9</i>	5'-GCTGACTACGATAAGGACGGCA-3'	5'-TAGTGGTGCAGGCAGAGTAGGA-3'
mouse <i>Tnf</i>	5'-GGTGCCTATGTCTCAGCCTCTT-3'	5'-GCCATAGAACTGATGAGAGGGAG-3'
mouse <i>Il6</i>	5'-TACCACTTCACAAGTCGGAGGC-3'	5'-CTGCAAGTGCATCATCGTTGTTC-3'
mouse <i>Ptgs2</i>	5'-GCGACATACTCAAGCAGGAGCA-3'	5'-AGTGGTAACCGCTCAGGTGTTG-3'
human <i>IL6</i>	5'-AGACAGCCACTCACCTCTTCAG-3'	5'-TTCTGCCAGTGCCTCTTTGCTG-3'
mouse <i>Nos2</i>	5'-GAGACAGGGAAGTCTGAAGCAC-3'	5'-CCAGCAGTAGTTGCTCCTCTTC-3'
human <i>NOS2</i>	5'-GCTCTACACCTCCAATGTGACC-3'	5'-CTGCCGAGATTTGAGCCTCATG-3'
mouse <i>Arg1</i>	5'-CATTGGCTTGCGAGACGTAGAC-3'	5'-GCTGAAGGTCTCTTCCATCACC-3'
mouse <i>Actb</i>	5'-CTGTCCCTGTATGCCTCTG-3'	5'-ATGTCACGCACGATTTCC-3'
human <i>ACTB</i>	5'-AGCGAG CATCCCCCAAAGTT-3'	5'-AGGGCA CGAAGGCTCATCATT-3'