**Supplemental Figure Legends:**

**Supplemental Figure 1.** Caerulein treatment had similar acute effects. Caerulein (50 μg/kg) was injected intraperitoneally at the time points shown (a). Histologic examination showed that within 24 hours after caerulein treatments, acute pancreatitis as indicated by edema and acinar cell vacuolization developed in both control (b) and Acinar-Ras mice (c, 100X, inset 400X). Measurements of pancreatitis parameters such as edema (d) and serum amylase (e) also indicated a similar extent of acute inflammation after initial caerulein treatments.

**Supplemental Figure 2. Inflammatory cell infiltration and fibrosis were evident in** caerulein-induced chronic pancreatitis in Acinar-Ras mice. 4 weeks after caerulein treatment pancreata of Acinar-Ras mice showed strong infiltration of leukocytes (a, 100X, inset 400X), mainly macrophages (b, 100X, inset 400X). Stroma replacement with positive collagen trichrome staining (c, 100X) and abundant smooth muscle actin expression (d, 100X, inset 400X) was observed in these animals. Total Ras was increased in acinar-Ras mice as compared with controls 4 weeks after caerulein treatment (e).

**Supplemental Figure 3.** Caerulein treatments resulted in prolonged elevation of Ras downstream signaling in the presence of mutant K-Ras. Phospho-Erk immunostaining indicated that increased Erk activity was localized in acinar derived cells of pancreata from Acinar-Ras mice (a) compared with control animals (b) at week 4 (100X, inset 400X). Caerulein caused prolonged elevation of phosphor-Erk in Acinar-Ras mice as detected by western blot (c).

**Supplemental Figure 4.** LPS treatments led to chronic inflammation and precancerous lesions in Acinar-Ras but not control mice. LPS (10 mg/kg) was injected intraperitoneally once per week for 4 consecutive weeks (a). Pancreata of control mice were histologically normal after LPS treatments (b, 100X). In contrast, pancreata of Acinar-Ras mice developed chronic pancreatitis and PanINs

within 4 weeks (c, 100X). Ras activity was strongly increased in pancreata of Acinar-Ras mice after 4 weeks of LPS treatments (d) (*$p<0.05$ versus non-treated Acinar-Ras mice).

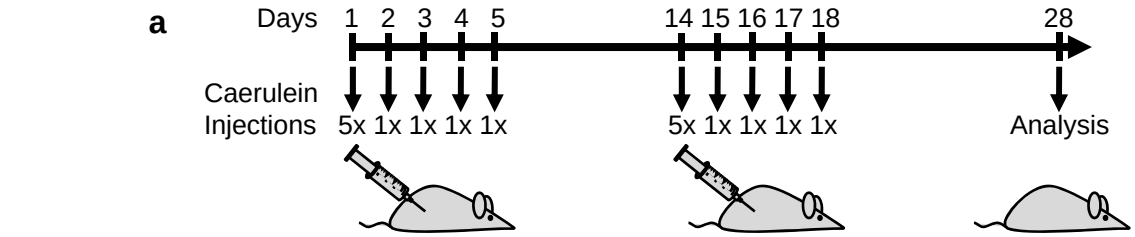
**Supplemental Figure 5.** NF-κB inhibitory subunit IκB-α was phosphorylated after caerulein induction in Acinar-Ras mice. After 2 series of caerulein treatments (week 4) increased phosphorylation of IκB-α was detected by phosphor-specific antibody against IκB-α in pancreata of Acinar-Ras mice (a, 200X) but not in controls (b, 200X).

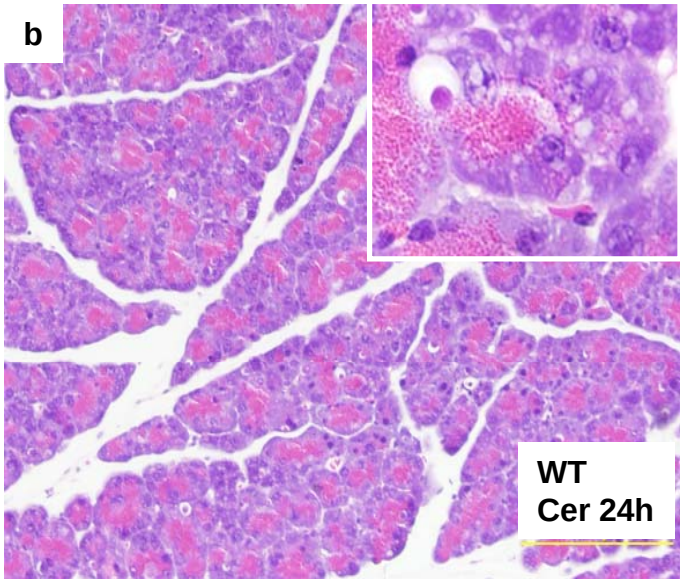
**Supplemental Figure 6.** Cox-2 expression in pancreatic acinar cells led to chronic pancreatitis and cancer in Acinar-Ras but not control mice. Pancreata of mice expressing Cox-2 alone were 2.5 times bigger than those of control littermates (a) (*$p<0.05$ compared to control mice, n=7 animals). Cox-2 alone induced development of acinar cell vacuolization and cyst formation which was observed after 8-months (b, 100X, inset 400X).

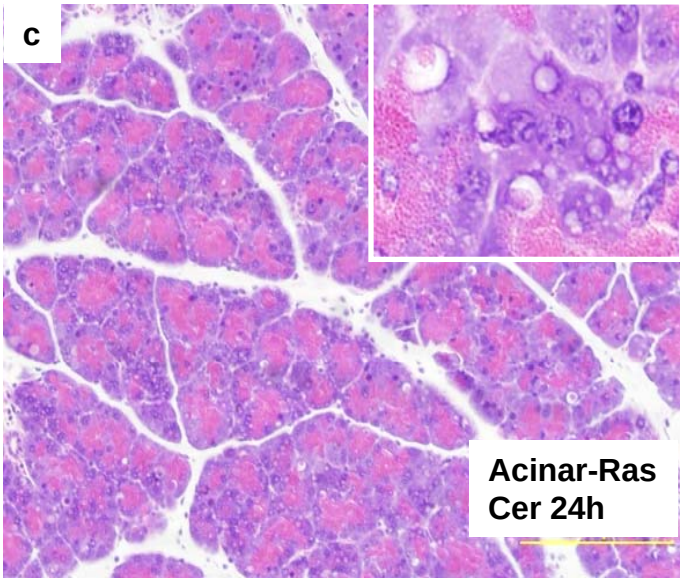
**Supplemental Figure 7.** Levels of active phospho-Erk increased in pancreata expressing both Cox-2 and mutant K-Ras. Phospho-Erk was examined by immunohistochemical staining in the pancreata expressing Cox-2. Cox-2 expression alone increased the level of phospho-Erk in many acinar cells (a, 100X). The expression of oncogenic K-Ras alone increased phospo-Erk levels only in the rare PanINs (b, 100X). The combination of expression of both Cox-2 and mutant K-Ras generated much higher levels of phospho-Erk in acinar derived cells of 2-month-old mice (c,100X).

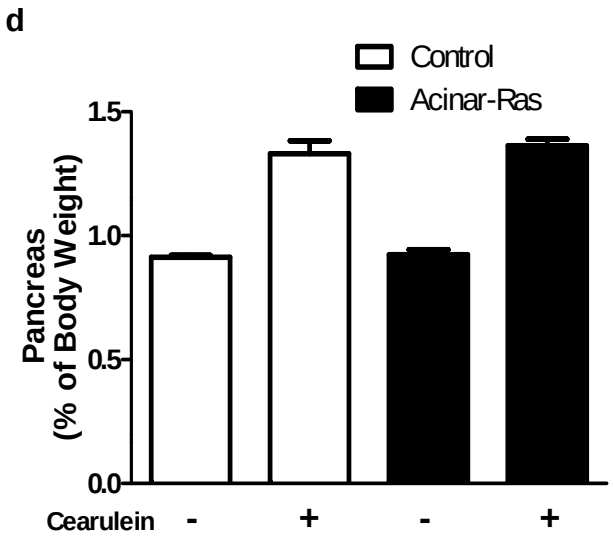
**Supplemental Figure 8.** Ras, Cox-2 and NF-κB pathways examination in normal human pancreatic tissues. p-Erk (a), Cox-2 (b), p65 translocation(c) and p-IκB-α (d) staining were not evident in normal pancreas as compared with the strong staining of these signaling molecules in human pancreatic cancer tissues shown in Figure 8.

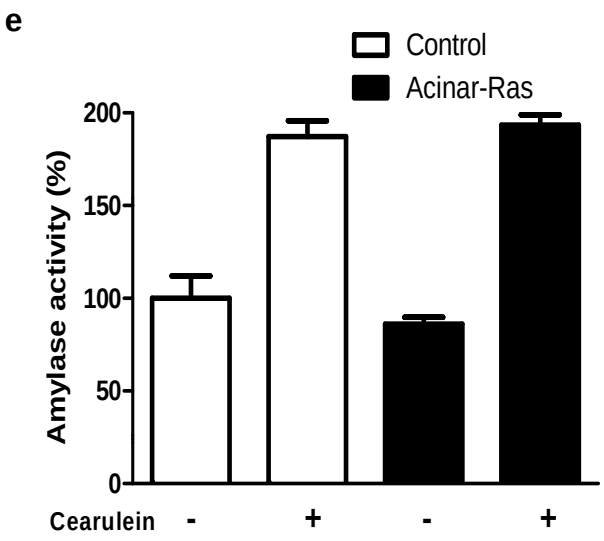
**Supplemental Figure 1**



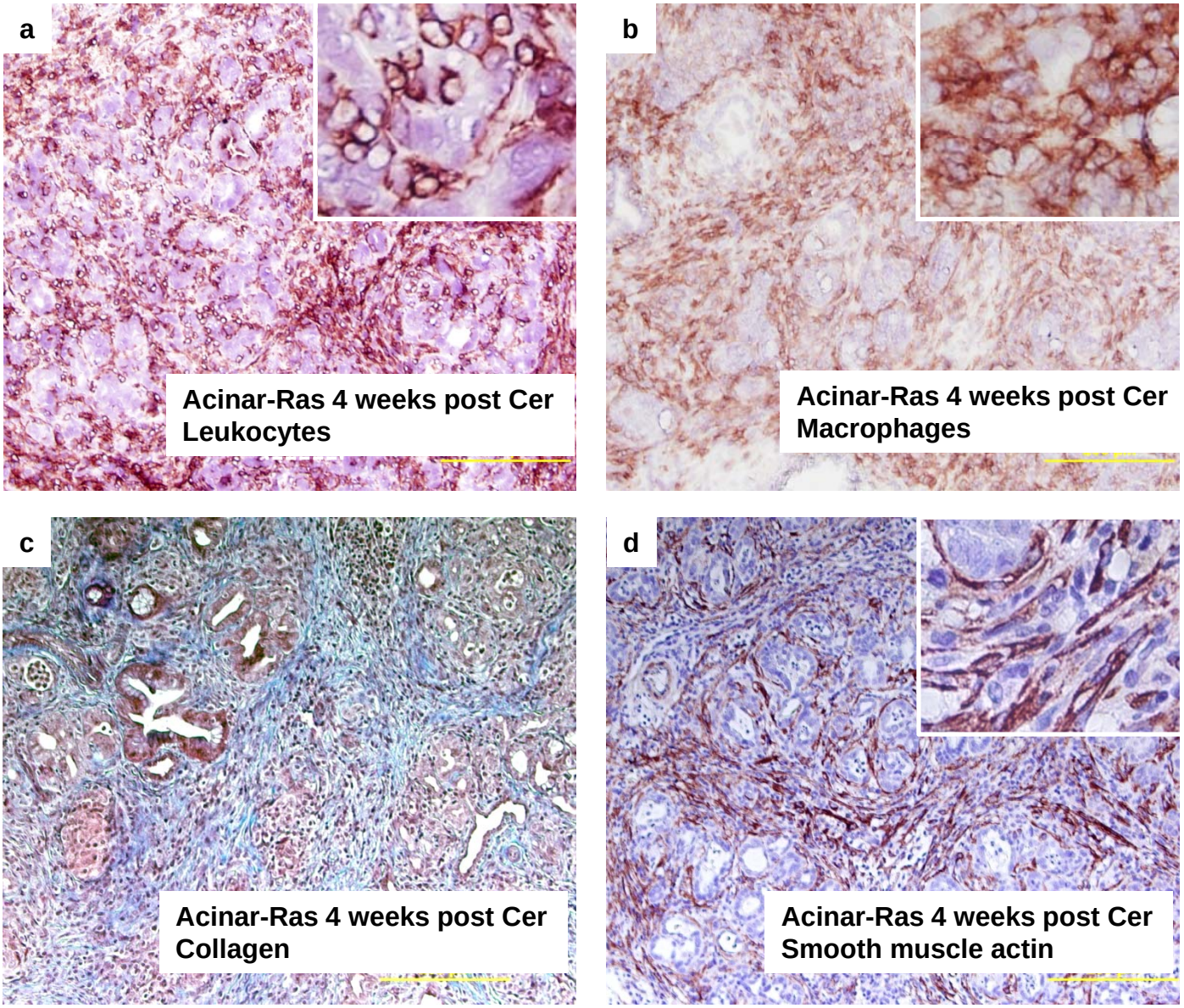



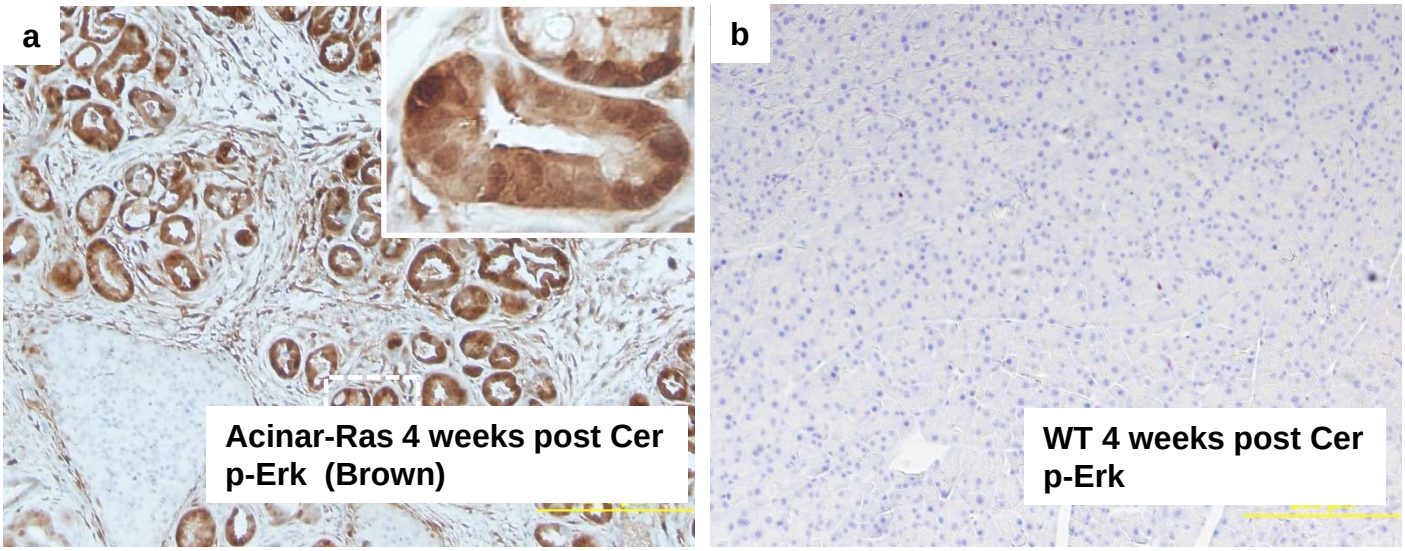



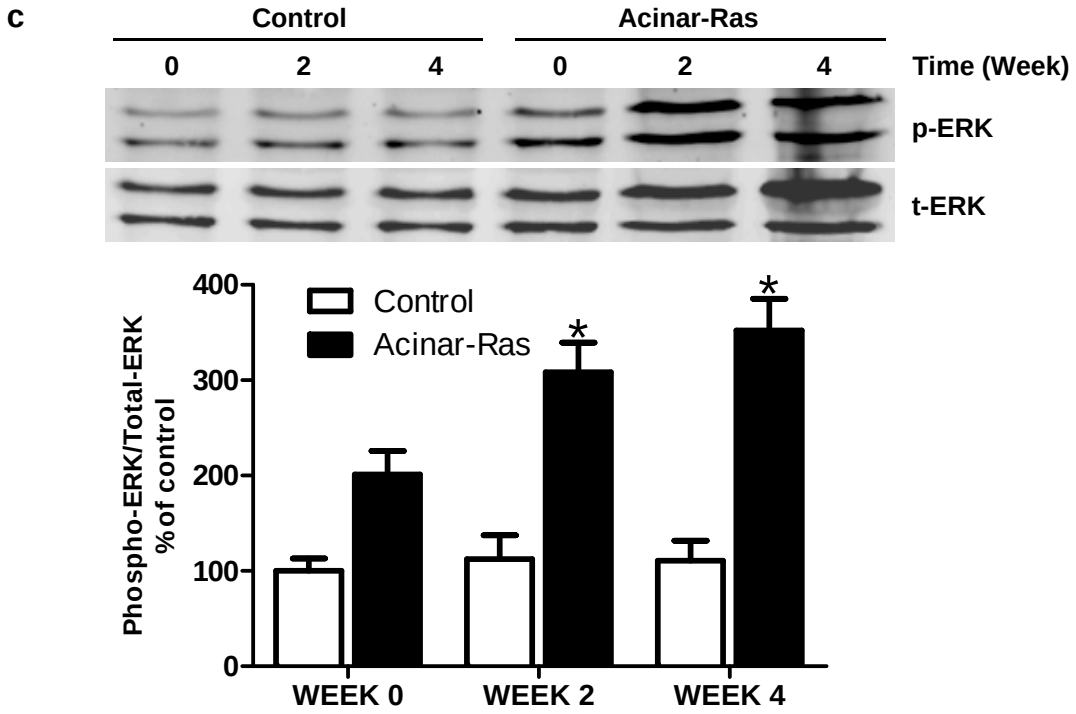



**Supplemental Figure 2**

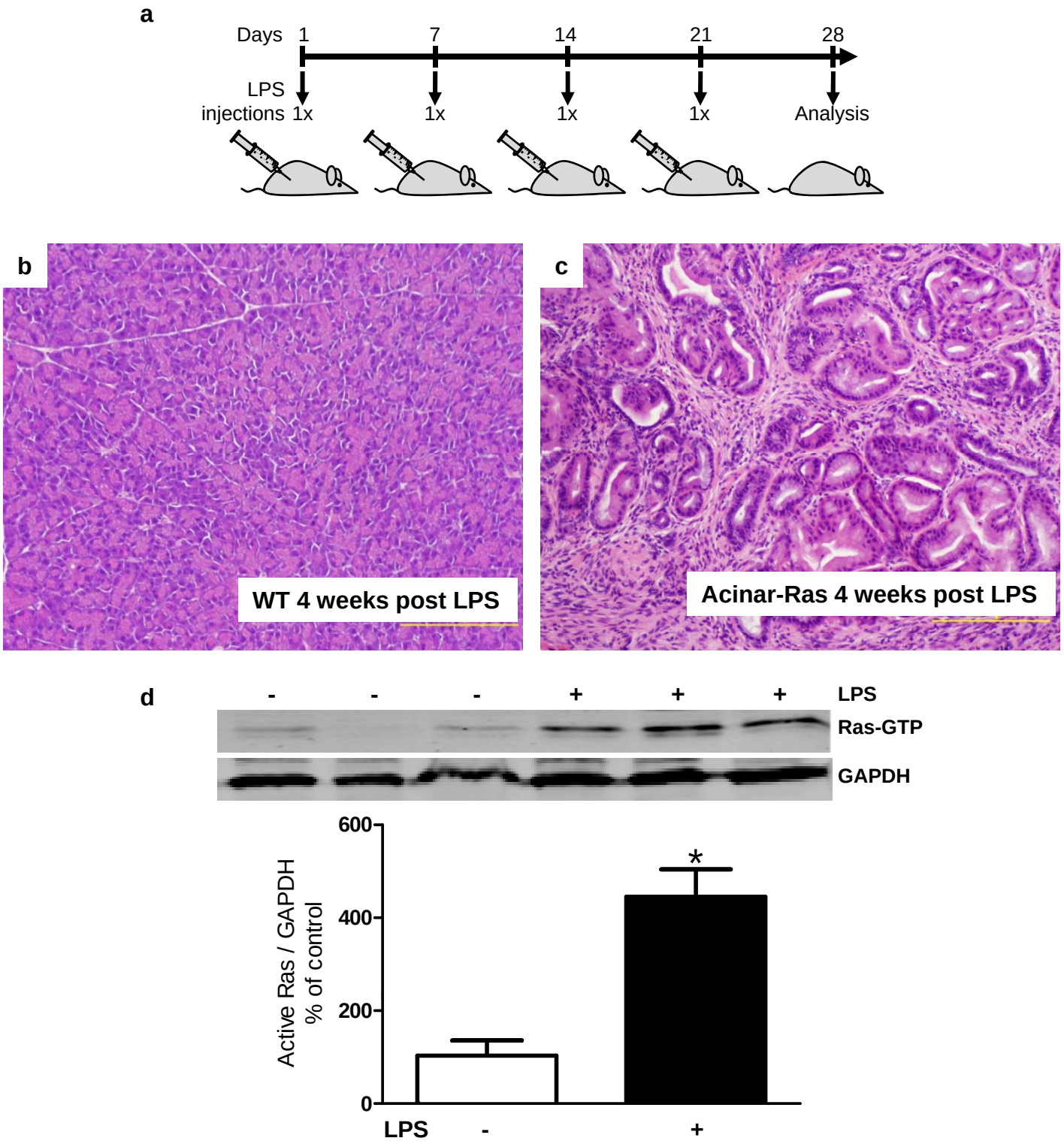


**Supplemental Figure 3**



**Supplemental Figure 4**



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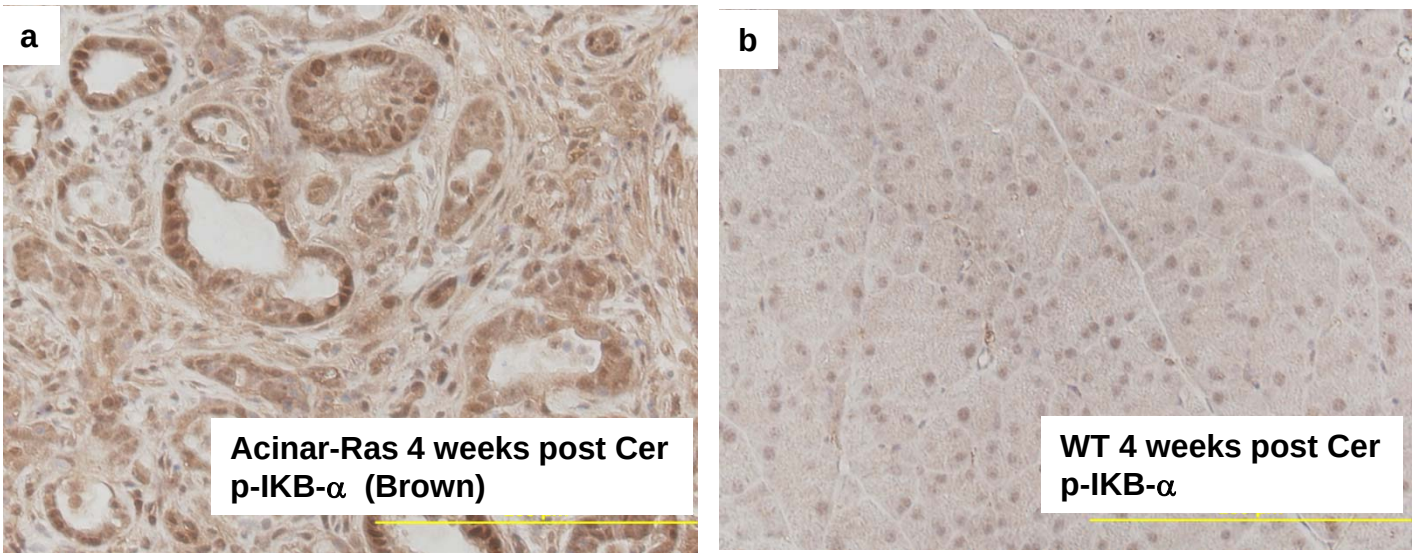
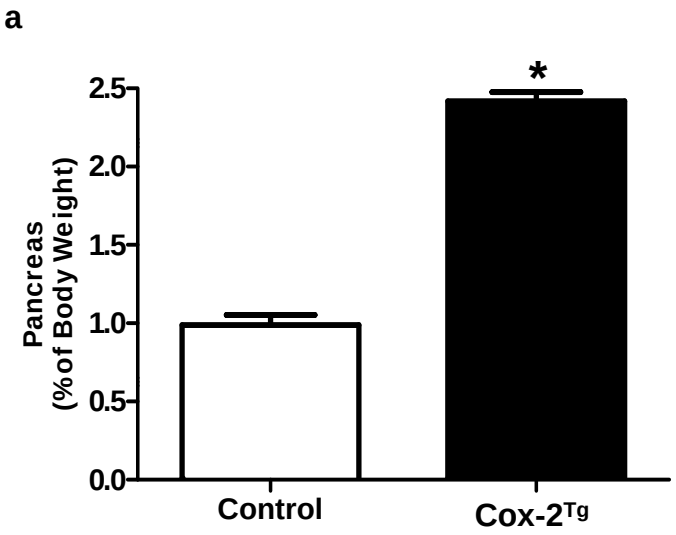
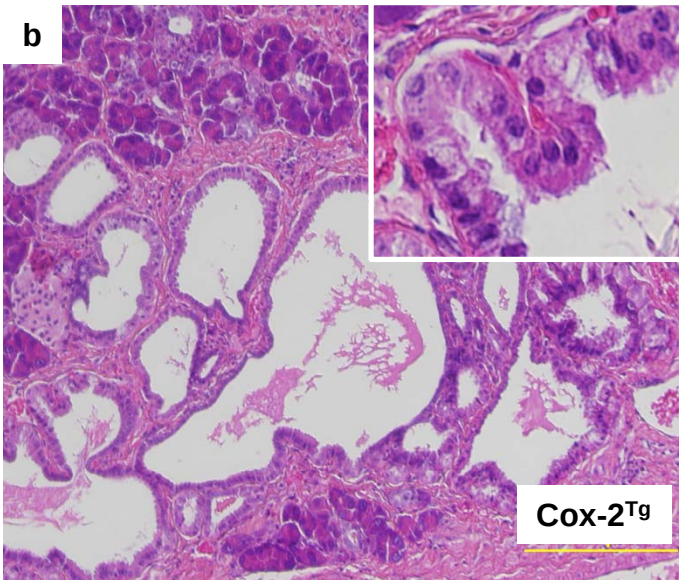
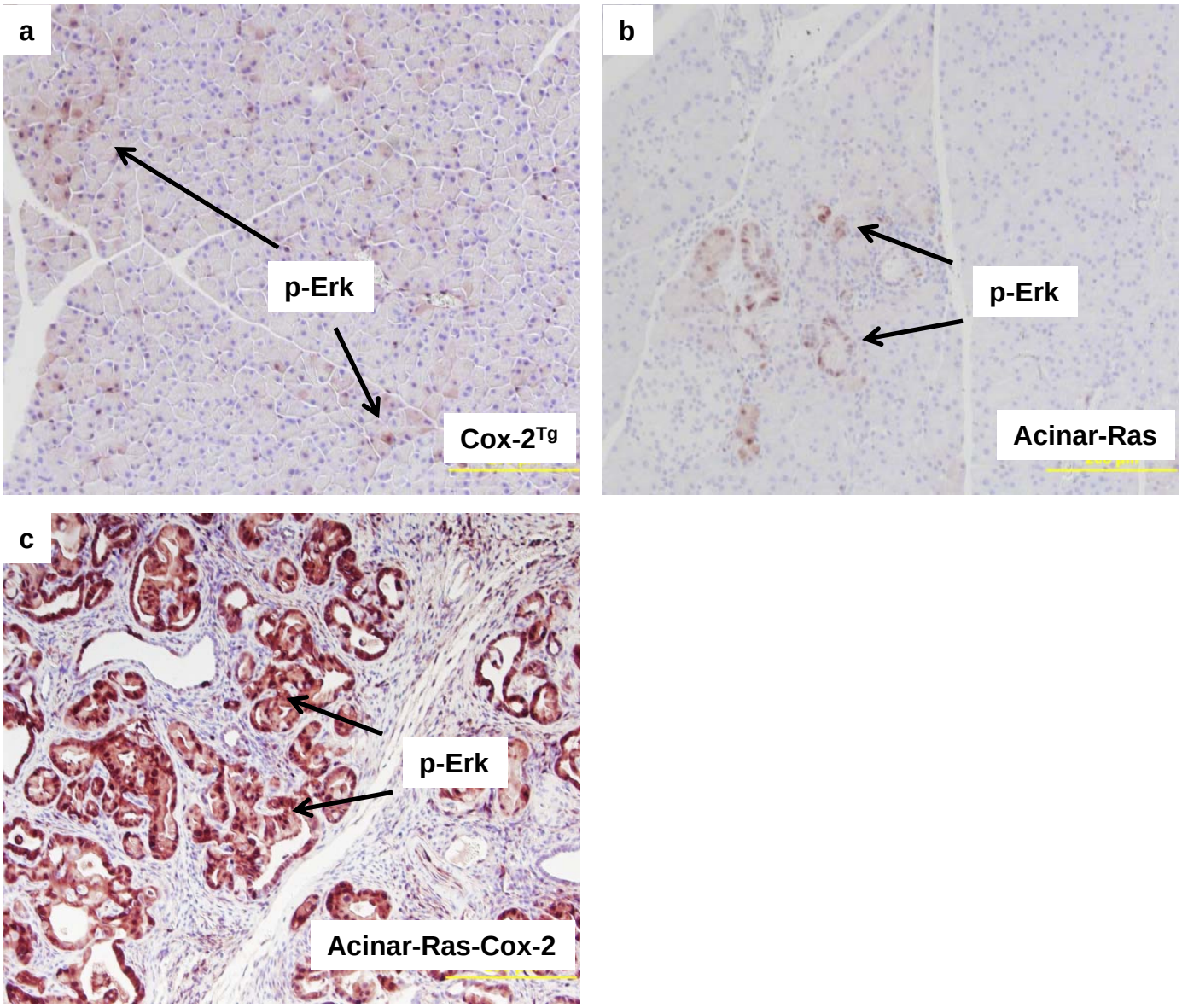


**Supplemental Figure 6**



**Supplemental Figure 7**



**Supplemental Figure 8**