

Supplementary Data:

Supplementary Figure legends

Supplementary Figures 1-7

Supplementary Figure legends

Supplementary Figure 1. Nr5a2 is downregulated in transient duct-like differentiation

(A) Nr5a2 staining of pancreata isolated at different time points (day 2 and 7) after pancreatitis induction or PBS injection of control mice; arrows mark Nr5a2 positive cells, arrowheads mark Nr5a2 negative cells. Upper panel: Immunohistochemistry staining for Nr5a2. Lower panel: Immunofluorescent co-staining of acinar tissue or transient duct-like lesions for CPA1, Clusterin and Nr5a2 during a pancreatitis time course in control mice: Clusterin positive ADM at day 2 after pancreatitis induction displays reduced expression levels of Nr5a2.

(B) RNA expression of Nr5a2 during indicated time points after pancreatitis induction in control mice. Expression is relative to PBS treated mice (=1); *p* values are relative to control, values are shown as mean \pm s.e.m. (A) Upper panel: scale bar 50 μ m. Lower panel: scale bar 10 μ m.

Supplementary Figure 2. Loss of Nr5a2 does not preclude pancreatic lineage development

(A) Upper panel: Immunofluorescent co-staining for CPA1 and Nr5a2 of P3 pancreas tissue of the indicated genotypes (arrow mark an example for a Nr5a2/CPA1 double positive cell; arrowhead marks a Nr5a2 negative acinar cell); scale bar 10 μ m. (B) H&E staining of postnatal day 3 (P3) pancreatic tissue of the indicated genotypes; scale bar 100 μ m. (C) Immunofluorescence staining marking

acinar (carboxypeptidase-1; CPA1), ductal (cytokeratin 19; CK19), and beta cells (insulin; INS) in P3 pancreata of the indicated genotypes; scale bar 50µm.

Supplementary Figure 3. Loss of Nr5a2 results in pancreatic atrophy after caerulein-induced pancreatitis

Macroscopic images of pancreata during a pancreatitis time course in control and *PdxCre^{late}; Nr5a2^{c/c}* mice.

Supplementary Figure 4. Absence of Nr5a2 leads to pancreatic hyperplasia in the context of oncogenic Kras

Pancreas weight to body weight ratio in 3 week old *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/+}* and *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/c}* mice (n=4-5 per group). Values are shown as mean ± s.e.m.

Supplementary Figure 5. Cultured *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/c}* pancreatic duct cells are efficiently recombined

Pancreatic duct cell (PDC) cultures were established from a 3 weeks old *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/c}* mouse. The established cell line was analyzed for recombination of the *Kras^{G12D}* and *Nr5a2^c* alleles. For reference, tail DNA analyses (not Cre recombined) of the indicated genotypes are shown. (A) PCR showing recombination of the *Nr5a2^c* alleles and (B) recombination of the *Kras^{G12D}* allele.

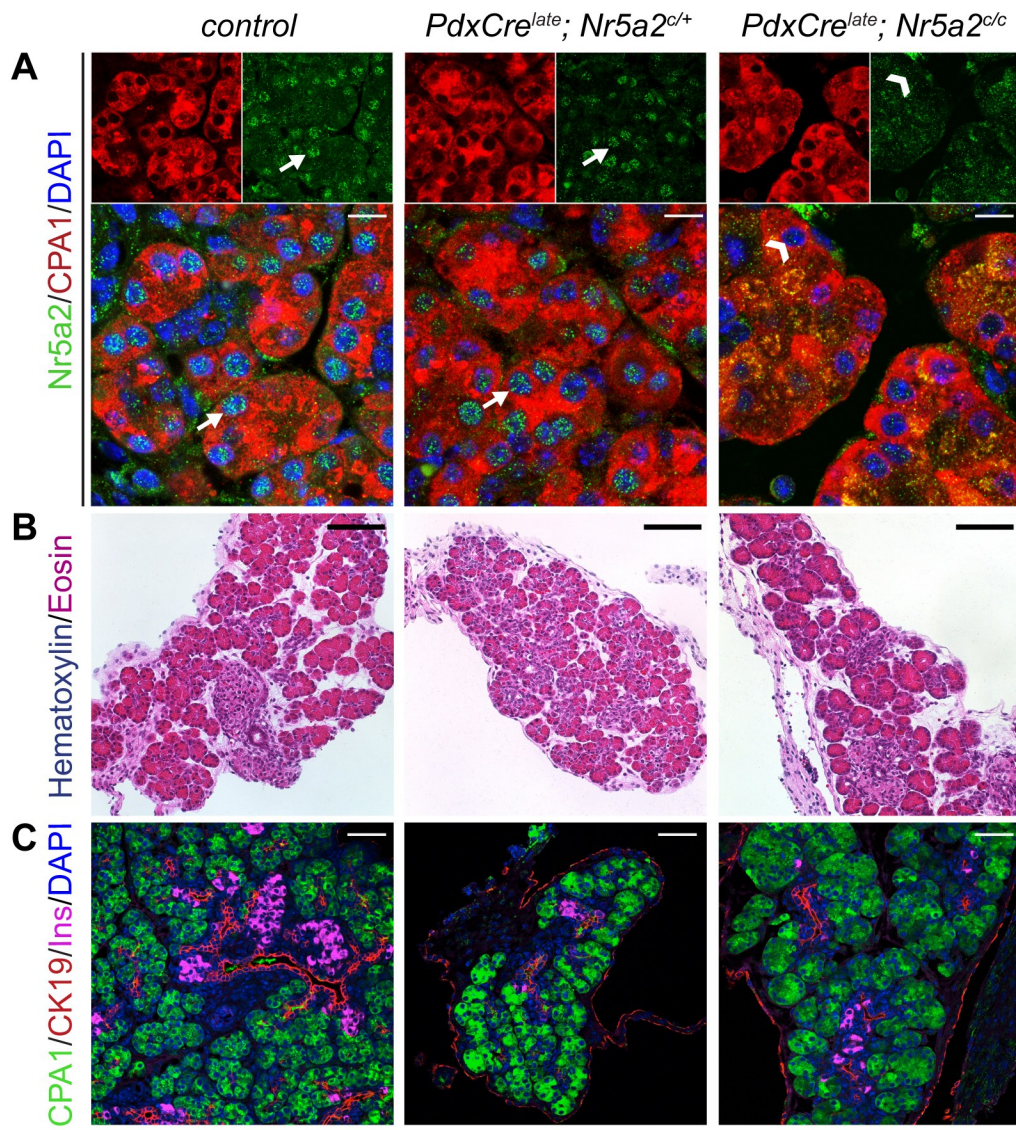
Supplementary Figure 6. *Nr5a2* heterozygosity accelerates oncogenic *Kras* driven preneoplastic transformation

(A) Representative H&E pictures of *PdxCre^{late}; Kras^{G12D}* and *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/+}* mice. Inset for *PdxCre^{late}; Kras^{G12D}* shows an early PanIN lesions, whereas inset for *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/+}* displays an advanced PanIN lesion. Scale bar 500µm. (B) Quantification of ADM and PanIN lesions. For the analysis 5 individual 100x pictures per mouse were quantified. A total of 5 *PdxCre^{late}; Kras^{G12D}* and 5 *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/+}* mice were analyzed. n.d. = not detected, *p* values represent *PdxCre^{late}; Kras^{G12D}* compared to *PdxCre^{late}; Kras^{G12D}; Nr5a2^{c/+}* mice for the respective lesions; values are shown as mean ± s.e.m. All analyses were performed on 12 weeks old mice.

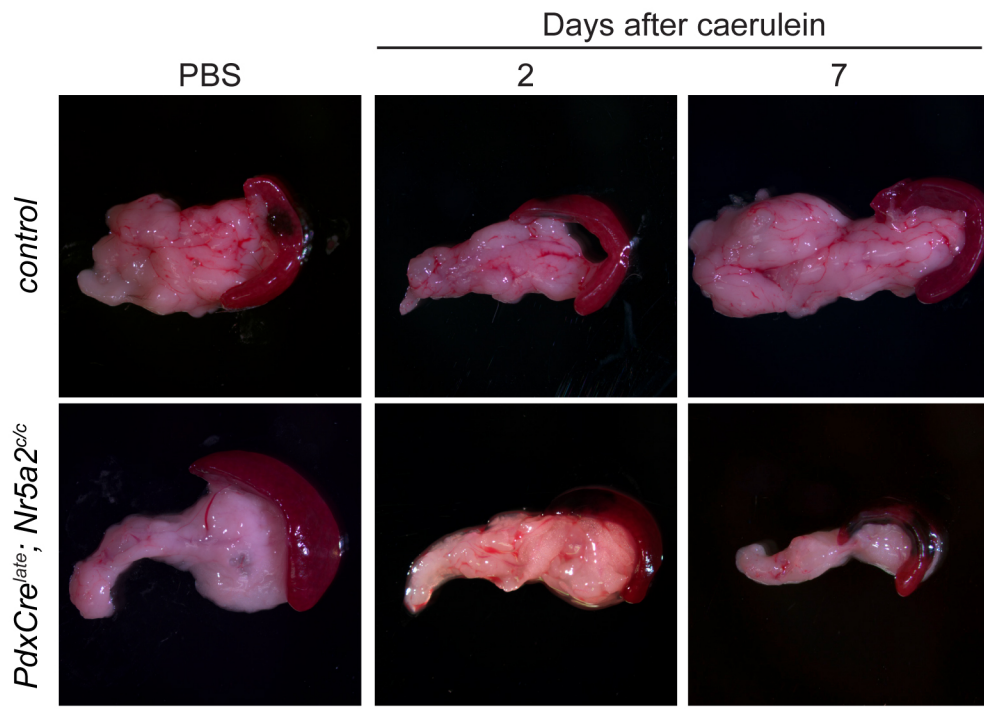
Supplementary Figure 7. *Nr5a2* deletion potentiates the inflammatory infiltrate around *Kras* driven preneoplastic lesions

CD45 staining of *Ptf1aCre^{ER}; Kras^{G12D}; Nr5a2^{c/+}; R26R^{EYFP}* and *Ptf1aCre^{ER}; Kras^{G12D}; Nr5a2^{c/c}; R26R^{EYFP}* pancreata 2 weeks after tamoxifen induction of the mice. The rare lesions in *Ptf1aCre^{ER}; Kras^{G12D}; Nr5a2^{c/+}; R26R^{EYFP}* mice display only few surrounding CD45 positive inflammatory cells, whereas sporadic *Nr5a2* deleted preneoplastic lesions show a marked inflammatory reaction. The inflammatory reaction is even more pronounced in more severely affected lobes with multiple preneoplastic lesions. Scale bar 250µm.

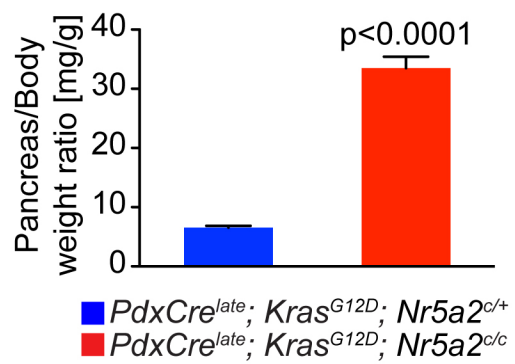
Supplementary Figure 2



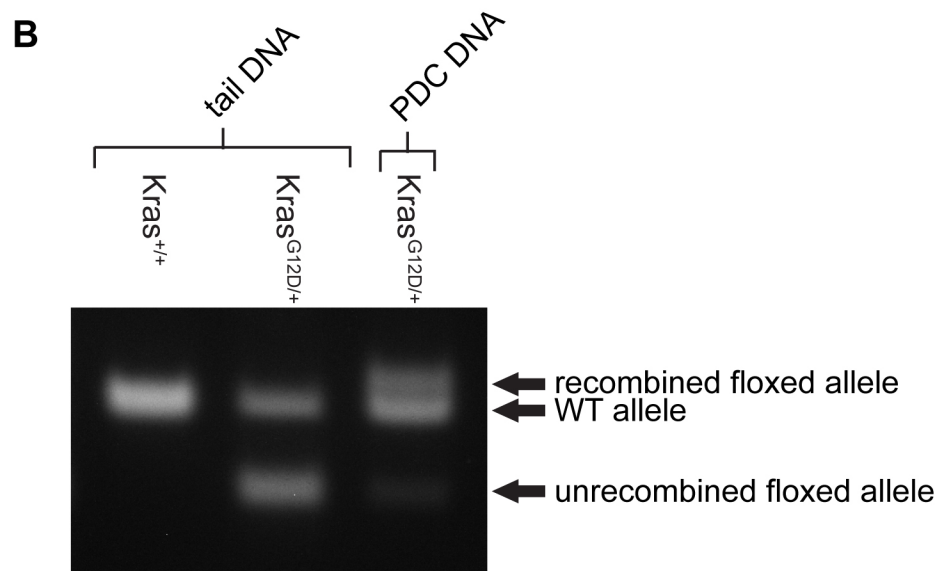
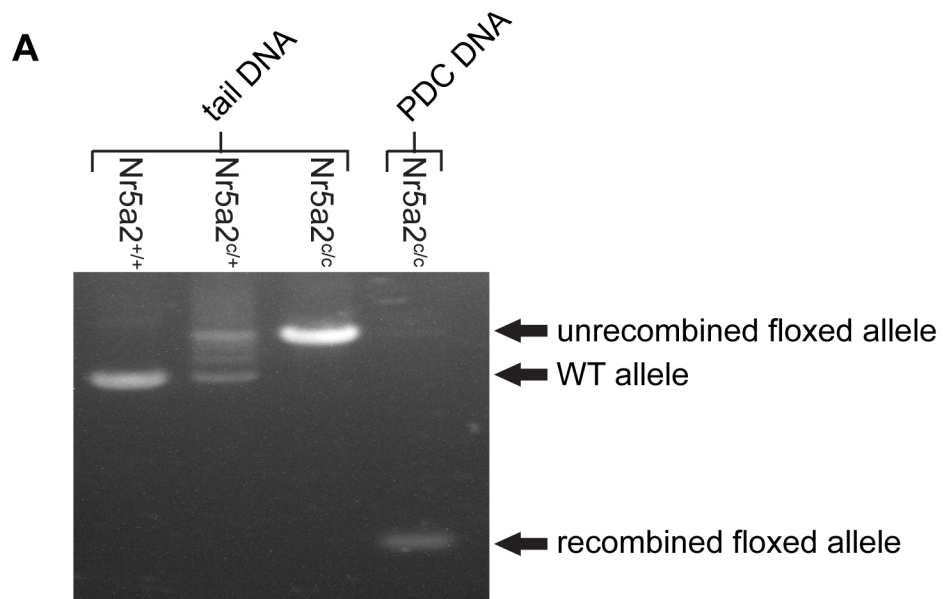
Supplementary Figure 3



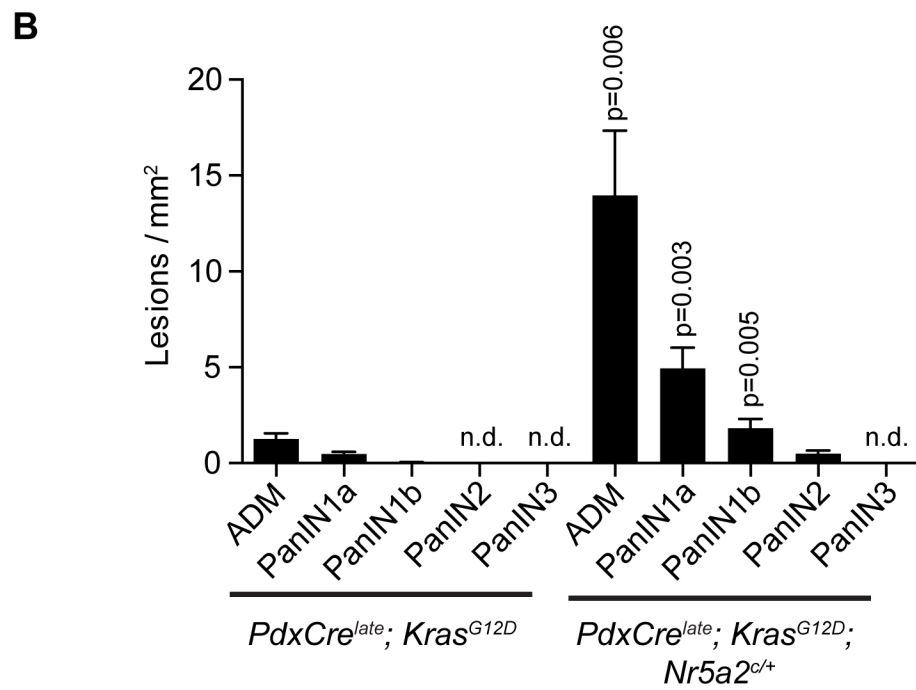
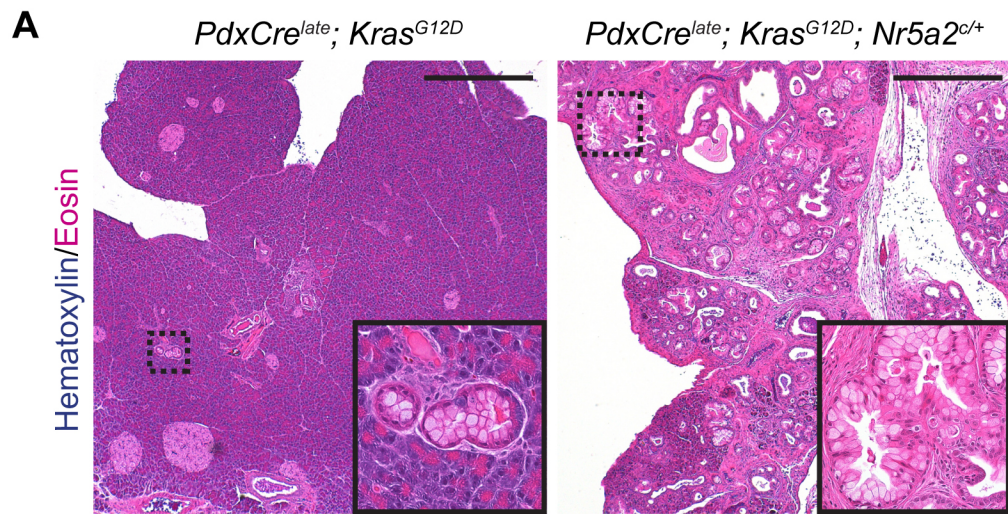
Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure 6



Supplementary Figure 7

