Supplementary materials and methods:

Soft agar assay

For soft agar assays, cells were seeded into 0.4% low melting point agarose (Lonza, Catalogue no: 50101) on top of 1% agarose layer. After 3 weeks, colonies were fixed in methanol and stained with crystal violet. For quantification crystal violet positive colonies were counted**.**

Flow cytometry analysis

Cells were trypsinized, spun down and re-suspended in FACS buffer (PBS with 2mM EDTA and 1% FBS). Blocking was performed by incubating the cells in Fc block for 30 minutes on ice. 1 ug primary antibody Sca1 (BD Pharmingen, Catalogue no: 557405) was used to label 10^6 cells. Cells were washed and re-suspended in FACS buffer followed by cell sorting.

Genotyping of cell lines

To analyze the recombination of the *Kras*^{G12D} allele, the protocol published by Dr. Tyler Jacks laboratory was used (http://web.mit.edu/jacks-lab/protocols/KrasCond_tablesTWO.html). To examine the recombination of the Brg1 allele the following primers were used as previously reported:

TH185 5-GTCATACTTATGTCATAGCC-3

TB82 5-GATCAGCTCATGCCCTAAGG-3

TG57 5-GCCTTGTCTCAAACTGATAAG-3

Subcutaneous tumor growth assay

$2x10^6$ cells were injected subcutaneously into both flanks of immune compromised NOD *scid* gamma mice. Mice were examined for the formation of

tumors on a daily basis and tumor volume was determined by measuring tumor length and width [tumor volume = ½ x tumor length x (tumor width) ^{2}] with electronic caliper. Mice were sacrificed and tumors were taken out when tumors started to show signs of ulceration.

RNA isolation and quantitative real time PCR

Cells were homogenized by QIAshredder (Qiagen, Catalogue no: 79656). RNA was isolated using RNA-easy kit (Qiagen, Catalogue no: 74104). cDNA was synthesized using Superscript III First-Strand Synthesis Kit (Invitrogen, Catalogue no: 18080). Q-PCR was performed with SYBR green-based gene expression assays (Roche, Catalogue no: 04913914001). Primers were designed through MGH primer bank. Primer sequences are available on request.

Chromatin immunoprecipitation

Cells were first cross-linked with 37% formaldehyde (Fisher, Catalogue no: F8775) to a final concentration of 1% and incubated for 10 min with gentle swirling at room temperature. Cross-linking was stopped by addition of 2.5 M glycine at a final concentration of 0.125 M glycine for 5 min with gentle swirling. Cells were washed twice with ice-cold sterile PBS and then collected by adding 1 ml of ice-cold sterile PBS containing protease inhibitors (Roche). Cells were collected and centrifuged at 2,000 rpm for 5 min. The cell pellet was then re-suspended in sodium dodecyl sulfate (SDS) lysis buffer (1% SDS, 10 mM EDTA, 50 mM Tris, pH 8.1) and placed on ice for 10 min. Extract was sonicated using Diagenode Bioruptor, pre-cleared, and immunoprecipitation was carried out with 2 µg of antibody (H3K27Ac, Abcam and immunoglobulin G, Santa Cruz). Cross-

links were reversed on all samples followed by RNase A treatment and proteinase K digestion. DNA was extracted from the digested samples using a PCR purification kit (Qiagen, Catalogue no: 28104). Extracted DNA was amplified by real-time PCR.

Western blotting

Cells were harvested following washing with PBS. Cells were lysed by suspension in 2 volumes of RIPA buffer with phosphatase and protease inhibitor cocktail. Extracts were subjected to sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis, followed by blotting to PVDF membrane. The blots were probed with antibodies to Brg1 (Santa Cruz, Catalogue no: sc-10768), E-cadherin (Cell signaling, Catalogue no: 3195), Vimentin (Cell signaling, Catalogue no: 5741), Hmga2 (Biocheck; Catalogue no: 59170AP), Actin (Santa Cruz, Catalogue no: sc47778) and GAPDH (Santa Cruz, Catalogue no: sc-25778).

Acinar cell isolation

Mouse pancreta were chopped into small pieces and digested with Collagenase P (0.4 mg/ ml). After two washes with HBSS buffer containing 5% FBS, tissue suspension was filtered through 100um cell strainer. The flow through was layered on HBSS + 30% FBS solution and centrifuged. Pellet was re-suspended into acinar cultured media with 1% FBS, infected with 300 MOI adenovirus expressing Cre recombinase and incubated overnight in low-attachment plates. Next day, cell pellet was centrifuged and re-suspended in 1:2 full acinar media: matrigel solution and plated on a rat-tail collagen Type I coated plate. Full acinar

media used was Waymouth's media + 10% FBS + 1% Penicillin/ Streptomycin + 100 ug /ml trypsin inhibitor + 1ug/ml dexamethasone.

Accession number:

The gene expression omnibus accession number for the RNA deep sequencing data reported in this manuscript is GSE65315.

Supplementary figure legends

Supplemental Figure 1:

(A) Schematic of pancreatic ductal cell isolation, culture and *in vitro* recombination. (B) Table listing the genotypes and genetic outcomes of mice strains used. (C) Quantitative PCR analysis of acinar, duct and endocrine cell differentiation markers in isolated pancreatic duct cell. (D and E) PCR analysis of $Kras^{G12D}$ (D) or Brg1f/*f* (E) alleles in PDC after adenovirus expressing Cre mediated recombination. Tail of a wild type mouse was used as a negative control for both (D) and (E). Genomic DNA from *Ptf1aCre;* $Kras^{G12D}$ derived tumor cell line was used as a positive control for (D). Genomic DNA from *Ptf1aCre;* $Kras^{G12D}$*; Brg1f/f* derived tumor cell line was used as a positive control for (E).

Supplemental Figure 2:

(A) FACS analysis of $Kras^{G12D}$ PDC using the Sca1 antibody. (B) Quantitative PCR analysis of duct cell differentiation markers in PDC sorted from $Kras^{G12D}$ pancreatic duct cells based on Sca1 expression. (C) Quantitative PCR analysis

of Brg1 in PDC sorted from *Kras^{G12D}; Brg1 f/f* pancreatic duct cells based on Sca1 expression. (D) Quantitative PCR analysis of Brg1 in *Kras^{G12D}; Brg1 f/f* PDC expressing empty vector or vector expressing wild type Brg1.

Supplemental Figure 3:

Immortalized PDC gives rise to pancreatic lesions in vivo

(A) Population doubling assay of wild type (WT), immortalized *Kras^{G12D}* and *Kras^{G12D}; Brg1 f/f* PDC. (B) Representative phase contrast micrograph of WT or immortalized *Kras^{G12D}* and *Kras^{G12D}; Brg1 f/f* PDC grown in 3D. (C) H & E and Krt19 stainings of immortalized PDC cells grown in 3D. Scale bar for H & E and Krt19 is 100um. (D) H & E, Krt19 and Ki67 stainings of immortalized PDC cells orthotopically transplanted into immune-deficient mice. Scale bar for H & E, Krt19 and Ki67 is 50um. (E) Detailed analyses of orthotopic tumors derived from *Kras^{G12D}* or *Kras^{G12D}; Brg1f/f* PDC.

Supplemental Figure 4:

DBA-lectin immunofluorescence stainings of control or 3 and 6 weeks old *Ptf1a Cre; Kras^{G12D}; Brg1 f/f* animals. Scale bar is 100um.

Supplemental Figure 5:

Quantitative PCR analysis of (A) *Brg1*, (B) *Pdx1* and (C) *Hnf4a* in subcutaneous tumors formed from IMPN-PDA cells expressing empty vector or vector expressing wild type Brg1. (D) % of Ki67 positive cells, (E) % of smooth muscle

actin positive area and (F) % of cleaved caspase 3 positive area in subcutaneous tumors formed from IMPN-PDA cells expressing empty vector or vector expressing wild type Brg1. Ten random fields from 3 mice in each group were chosen for quantification. (G) H & E stainings of control or Brg1 over-expressing tumors depicting less differentiated nature of Brg1 over-expressing lesions. Scale bar is 250 um.

Supplemental Figure 6:

Brg1 expression is higher in IPMN derived PDA compared to its precursor lesions. (A), (B) and (C) Representative Brg1 stainings in low-grade IPMN, high-grade IPMN and IPMN associated PDA human tissue samples. (D) Brg1 labeling scores from low-grade IPMN, high-grade IPMN and IPMN associated PDA samples. p value was calculated using one way anova.

Supplemental Figure 7:

Quantitative PCR analysis of Hmga2 in subcutaneous tumors formed from IMPN-PDA cells expressing empty vector or vector expressing wild type Brg1.

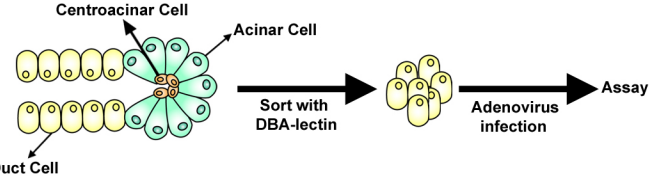
Supplemental Figure 8:

Brg1 plays critical roles in oncogenic Kras driven acinar ductal dedifferentiation. (A) Quantitative PCR analysis of acinar, duct and endocrine cell differentiation markers in isolated pancreatic acinar cell. (B) Representative pictures of acini cultured for 5 days following treatment with adenovirus expressing Cre

recombinase. Arrowheads indicate cells that underwent ADM and arrows indicate remnant acinar cells. (C) Quantification of ADM events/ well for the indicated genotypes. (D), (E) and (F) Quantitative PCR analysis of *Krt19*, *Amy* and *Brg1* expression in acinar cells isolated from *KrasG12D* and *KrasG12D; Brg1 f/f* mice at days 0 and 5.

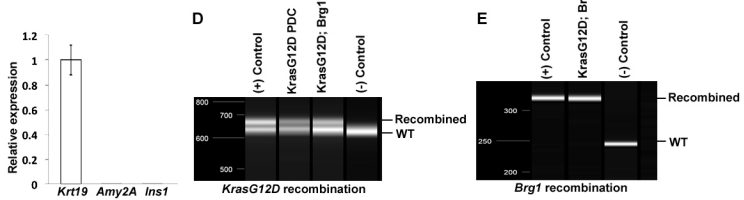
Supplemental Figure 1

A

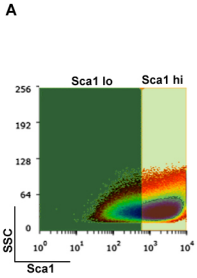


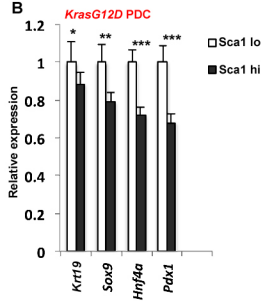
B

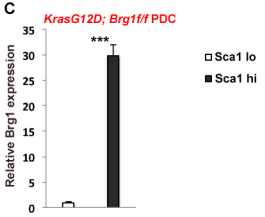
Genotype	Genetic outcome
Brg1 f/f	Deletion of Brg1 exons 2 and 3
LSL KrasG12D	Expression of oncogenic Kras
Sox9OE	Over-expression of HA tagged Sox9
Hnf1β Cre ERT²	Tamoxifen inducible expression of Cre from Pancreatic duct cells
Ptf1a Cre	Cre expression in embryonic pancreas 10.5 days

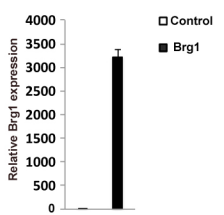


Supplemental figure 2

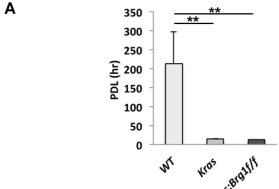


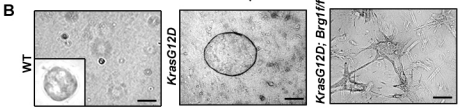


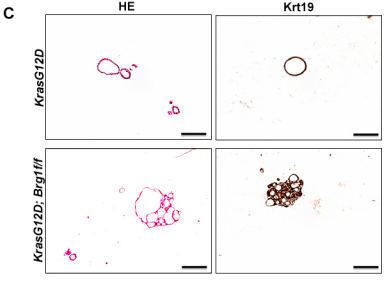


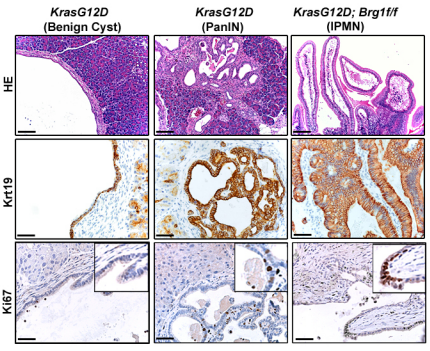


Supplemental Figure 3









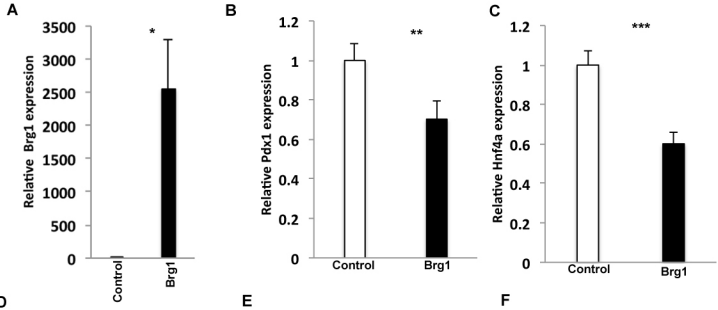
E

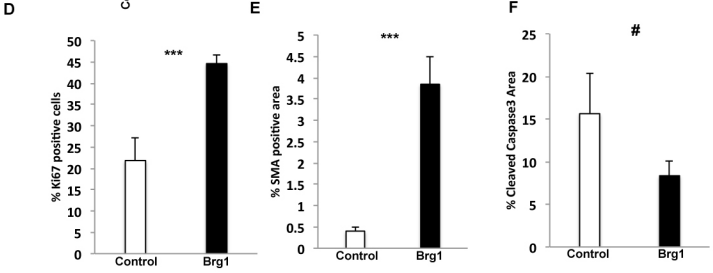
Genotype	PanIN	Cyst
KrasG12D	4/4	2/4
KrasG12D; Brg1f/f	0/4	2/3

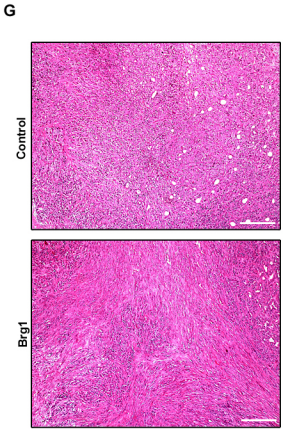
CK19	+	+	+
Ki67	+++	+	+++
Mucin	+	-	+

Supplemental figure 4

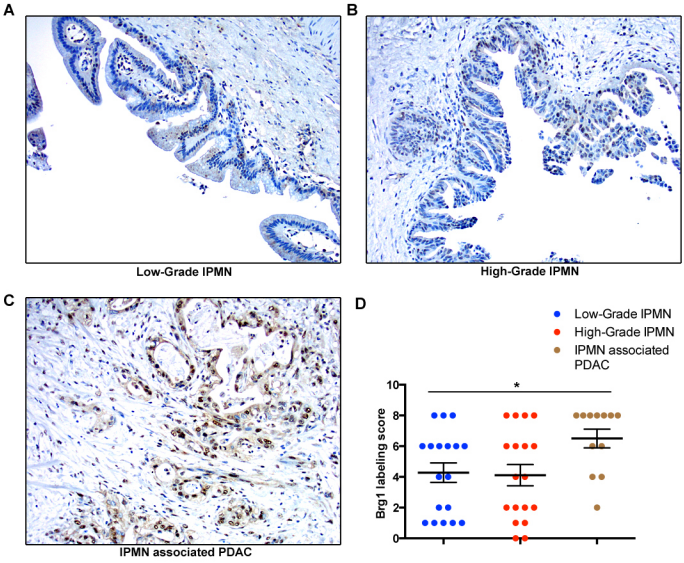
Supplemental Figure 5







Supplemental Figure 6



Supplemental Figure 7

Supplemental Figure 8