

Methods S1. Primers used in this study for cloning and sequencing. Related to STAR Methods.

Primer	Sequence
attB1-SpeI-HindIII-(N-HA)-KRAS ^{G12D} -fwd	aaaaagcaggcttcactagtgtctttcataagcttatgtatccatgatgatgtgcccgact
attB2-KRAS ^{G12D} -rev	agaaagctgggtgtgacacacattccacagggt
attB1-SpeI-HindIII-GNAS(EE) ^{R201H} -fwd_new	aaaaagcaggcttcactagtgtctttcataagcttatgggctgcctcggaac
attB2-GNAS ^{R201H} -rev_new	agaaagctgggtgtagagcagctctgactgacg
attB1-Luc2-for	aaaaagcaggcttcgccaccatggaagatgcaaaa
attB2-Luc2-rev	agaaagctgggtgttacacggcgatcttgccgccttc
attB1-adapter-primer (Gloeckner et al., 2009)	ggggacaagttgtacaaaaagcaggct
attB2-adapter-primer (Gloeckner et al., 2009)	ggggaccactttgtacaagaaagctgggt
PB-seq-fwd	agctcgttagtgaaccgtcagatc
PB-seq-rev	gtacaagaaagctgggt
GNAS_AS189-fwd	aatatatgccgaccgagcagg
Luc2_AS215-fwd	cgcttgtgtccgattcagtc
crRNA- <i>CDKN2A</i> exon2	GTAGGGGTAATTAGACACCT
crRNA- <i>CDKN2A</i> exon3	GTCTCGAGTCTATCGATATG
<i>CDKN2AKO</i> -external-fwd	GCGCTTGGATATACAGCAGTG
<i>CDKN2AKO</i> -external-rev	ACAGGAGCATCTCCCAACC
<i>CDKN2AKO</i> -internal-fwd	GGCATTGTGAGCAACCACTG
<i>CDKN2AKO</i> -internal-rev	CCTGTAGGACCTTCGGTGAC
GNAS-exon8-fwd (Salinas-Souza et al., 2015)	CCAGACCTTTGCTTTAGATTGG
GNAS-exon9-rev (Wood et al., 2017)	CACAGCATCCTACCGTTGAAG

Methods S2. Composition of solutions for ion secretion and uptake experiments. Related to STAR Methods “pH measurements via fluorescence microscopy”.

	Standard HEPES	Na-Free HCO ₃ ⁻	Standard HCO ₃ ⁻	NH ₄ Cl·HCO ₃ ⁻
NaCl [mM]	130	-	115	95
KCl [mM]	5	5	5	5
MgCl ₂ [mM]	1	1	1	1
CaCl ₂ [mM]	1	1	1	1
Hepes [mM]	10	-	-	-
Glucose [mM]	10	10	10	10
NaHCO ₃ ⁻ [mM]	-	-	25	25
NH ₄ Cl [mM]	-	-	-	20
NMDG [mM]	-	115	-	-
Choline HCO ₃ ⁻ [mM]	-	25	-	-
Atropine [mM]	-	0.01	-	-

Methods S3. Self-designed or commercially available qPCR primers used in this study. Related to STAR Methods “RNA isolation, reverse transcription and qPCR”.

Gene	Forward primer sequence (fwd)	Reverse primer sequence (rev)	QuantiTect Cat#
<i>ALB</i>	-	-	QT00063693*
<i>AMY2A</i>	-	-	QT01680595*
<i>BAX</i>	tggagctgcagaggatgattg	gaagttgccgtcagaaaacatg	
<i>CFTR</i>	-	-	QT00070007*
<i>FN1</i>	-	-	QT00038024*
<i>GCG</i>	-	-	QT00091756*
<i>HMBS</i>	-	-	QT00494130*
<i>INS</i>	-	-	QT01531040*
<i>KRAS</i>	-	-	QT00083622*
<i>KRT19</i>	ctacagccactactacacgac	cagagcctgttccgtctcaaa	
<i>KRT7</i>	ggagccgtgaatatctctgtga	tgcggtccggatggaataag	
<i>N-CAD</i>	-	-	QT00063196*
<i>NKX6-1</i>			QT00092379*
<i>P21</i>	gcgcatgtcagaaccgcct	gcaggcttctgtggcgga	
<i>PDX1</i>	-	-	QT00201859*
<i>PTF1A</i>	-	-	QT01033396*
<i>RELA</i>	atagaagagcagcgtgggga	ttgggggcacgattgtcaaa	
<i>SLUG</i>	cagtgattattccccgtatc	ccccaaagatgaggagtatc	
<i>SNAIL</i>	gctccttcgtccttctcctc	tgacatctgagtggtctgg	
<i>SOX4</i>	-	-	QT00220605*
<i>SOX9</i>	-	-	QT00001498*
<i>TWIST1</i>	ctagatgtcattgtttccagag	ccctgtttcttgaatttgg	
<i>VIM</i>	gacaatgcgtctctggcacgtctt	tctcgcctcctgcaggttctt	
<i>ZEB1</i>	aaagatgatgaatgcgagtc	tccatttcatcatgaccac	

*Primer sequences for commercial Qiagen primers are not available.

Methods S4. IHC/IF conditions for antibodies used in this study. Related to STAR Methods “IF and IHC staining on paraffin tissue sections” and “IF staining on cryo sections”.

Embedding	Antibody	Species	Company	Catalogue no.	Condition	Dilution
paraffin	ActTUB	rabbit	Abcam	ab179484	MW Citrat	1000
paraffin	AMY2A	rabbit	Sigma	A8273-1VL	MW Citrat	300
paraffin	C-pep	rabbit	Cell Signaling	4593	MW Citrat	100
paraffin	CA19-9	mouse	Thermo	116-NS-19-9	MW Citrat	500
paraffin	CDX2	rabbit	Cell Marque - RabMab	MU392-UC	MW Citrat	500
paraffin	CFTR	mouse	R&D	MAB1660	ST Tris	200
paraffin	CLDN1	rabbit	Abcam	ab15098	ST Tris	100
paraffin	E-CAD	mouse	Dako	M3612	PC Citrat	100
paraffin	E-CAD	mouse	BD Bioscience	610182	MW Citrat	1000

paraffin	GCG	mouse	Sigma	G2654	MW Citrat	500
paraffin	GFP	rabbit	Thermo	A6455	No AGR	1500
paraffin	H-NUCL	mouse	Abcam	ab190710	MW Citrat	200
paraffin	HA-Tag	rabbit	Cell Signaling	3724	MW Citrat	500
paraffin	HNF1B	mouse	Abcam	ab236759	MW Citrat	100
paraffin	Ki-67	rabbit	Thermo	MA5-14520	MW Citrat	100
paraffin	Ki-67	mouse	Dako	M7240	MW Citrat	200
paraffin	KRT19 (IF)	mouse	Dako	M0888	MW Citrat	100
paraffin	KRT19 (IHC)	mouse	Dako	M0888	Pronase	100
paraffin	KRT7 (IF)	mouse	Dako	M7018	MW Citrat	200
paraffin	KRT7 (IHC)	mouse	Dako	M7018	Pronase	200
paraffin	KRT8	mouse	BD Bioscience	345779	ST Tris	100
paraffin	mCherry	rabbit	Abcam	ab167453	No AGR	500
paraffin	MUC1	mouse	Santa Cruz	sc-7313	MW Citrat	100
paraffin	MUC5AC	mouse	Santa Cruz	sc-33667	MW Citrat	50
paraffin	N-CAD	rabbit	Cell Signaling	13116	MW Citrat or ST Tris	100
paraffin	NKX6-1	mouse	Developmental Studies Hybridoma Bank (DSHB)	F55A12 (concentrate)	MW Citrat	150
paraffin	P21	rabbit	Abcam	ab109520	MW Citrat	300
paraffin	P53	mouse	Santa Cruz	sc-47698	MW Citrat	100
paraffin	PDX1	goat	R&D	AF2419	MW Citrat	500
paraffin	PKC	rabbit	Abcam	ab59364	MW Citrat	200
paraffin	pRB	rabbit	Cell Signaling	8516	ST Citrat	200
paraffin	RB	mouse	Cell Signaling	9309	ST Citrat	400
paraffin	SOX9	rabbit	Millipore	AB5535	MW Citrat	500
paraffin	Turbo GFP	Rabbit	Thermo	PA5-22688	ST Tris	250
paraffin	VIM	rabbit	Cell Signaling	5741S	MW Citrat	500
paraffin	Zeb1	rabbit	Santa Cruz	sc-25388	PC Citrat	300
paraffin	ZO1	mouse	Thermo	33-9100	MW Citrat	500
cryo	C-pep	rabbit	Cell Signaling	#4593	No AGR	100
cryo	CD31	rat	BD Bioscience	557355	No AGR	100
cryo	CTRC	mouse	Millipore	MAB1476	No AGR	1200
cryo	GCG	mouse	Sigma	G2654	No AGR	500
cryo	E-CAD	rabbit	Cell Signaling	3195	No AGR	200
cryo	KRT7	mouse	Dako	M7018	No AGR	200
cryo	KRT8	mouse	BD Bioscience	345779	No AGR	100
cryo	KRT19	mouse	Dako	M0888	No AGR	100
cyro	CFTR	rabbit	Alomone	ACL-006	HB 94°C Citrat/Tween	200
cyro	Occludin	mouse	Thermo	33-1500	HB 94°C Citrat/Tween	200

*MW, microwave; No AGR, no antigen retrieval; PC, pressure cooker; ST, steamer; HB, heating block;