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Corresponding author(s): Rugang Zhang

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Flowjo was used to determine percentages of apoptotic cells. Images were analyzed using Live Imaging 4.0 software.
Data analysis	Prism 7 for Mac was used for calculating p values.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The ChIP-seq data was submitted to the Gene Expression Omnibus (GEO) database and can be accessed using accession number: GSE111841

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	For in vivo experiments, the sample size was determined based on the data obtained from in vitro experiments. The sample size for in vivo genetic pancreatic cancer mouse model experiments was 10 mice per group. For xenograft model, the sample size was 9 mice per group.
Data exclusions	There was no exclusion from the experiments.
Replication	All attempts at replication were successful.
Randomization	Experiments were all randomized.
Blinding	Analysis was performed blindly.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☐	☒ Research animals
☒	☐ Human research participants

Antibodies

Antibodies used	The following antibodies were purchased from the indicated suppliers: rabbit monoclonal anti-AMPK (Cell Signaling, Cat. No. 2532, 1:1000 for immunoblot), mouse monoclonal anti-b-actin (Sigma, Cat. No. A5441, 1:10000 for immunoblot), rabbit polyclonal anti-Cyclin A (Santa Cruz Biotechnology, Cat. No. sc-751, 1:1000 for immunoblot), mouse monoclonal anti-FLAG (Sigma, Cat. No. F3165, 1:1000 for immunoblot), mouse monoclonal anti-gH2Ax (Millipore, Cat. No. 05-636, 1:1000 for immunoblot), rabbit polyclonal anti-H3K27Ac (Millipore, Cat. No. 07-360, 1:1000 for ChIP), rabbit polyclonal anti-H3K4Me1 (Abcam, Cat. No. ab8895, 1:1000 for ChIP), rabbit monoclonal anti-HMGA1 (Abcam, Cat. No. 129153, 1:1000 for immunoblot and ChIP), rabbit polyclonal anti-HMGA2 (Abcam, Cat. No. 97276, 1:1000 for immunoblot), rabbit polyclonal anti-IgG (Santa Cruz, Cat. No. sc-2027, 1:1000 for ChIP), rabbit polyclonal anti-NAMPT (Bethyl Laboratories, Cat. No. A300-372A, 1:1000 for immunoblot), rabbit monoclonal anti-p-AMPK (Cell Signaling, Cat. No. 4188, 1:1000 for immunoblot), rabbit polyclonal anti-p-p38 (Cell Signaling, Cat. No. 9211, 1:1000 for immunoblot), rabbit polyclonal anti-p-p53 (Cell Signaling, Cat. No. 9284, 1:1000 for immunoblot), mouse monoclonal anti-p-p65 (Cell Signaling, Cat. No. 3036, 1:1000 for immunoblot), mouse monoclonal anti-p16 (Santa Cruz Biotechnology, Cat. No. sc-56330, 1:1000 for immunoblot), mouse monoclonal anti-p38 (Cell Signaling, Cat. No. 9228, 1:1000 for immunoblot), mouse monoclonal anti-p53 (Millipore, Cat. No. OP43, 1:1000 for immunoblot), rabbit monoclonal anti-p65 (Cell Signaling, Cat. No. 8242, 1:1000 for immunoblot), mouse monoclonal anti-RAS (Becton Dickinson, Cat. No. 610001, 1:1000 for immunoblot), mouse monoclonal anti-V5 (Invitrogen, Cat. No. 46-0705 for immunoblot).
Validation	The antibodies were validated according to the manufacturer.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	IMR90 normal primary human embryonic lung fibroblasts. TOV21G ovarian cancer cell line
Authentication	Cell lines were re-authenticated by The Wistar Institute's Genomics Facility using short tandem repeat profiling using AmpFLSTR Identifiler PCR Amplification kit (Life Technologies).

Mycoplasma contamination	Regular Mycoplasma testing was performed using LookOut Mycoplasma PCR detection (Sigma).
Commonly misidentified lines (See ICLAC register)	No cell lines used in this study were found in the database of commonly misidentified cell lines that is maintained by ICLAC and NCBI Biosample.

Research animals

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Animals/animal-derived materials	LSL-KRasG12D and p48-Cre mice were gifts from Dr. T. Jacks (Massachusetts Institute of Technology, Cambridge, Massachusetts, USA) and Dr. D. Bar-Sagi (NYU School of Medicine, New York, NY, USA), respectively. Mice are on a mixed background. At 8 weeks of age, mice received daily intraperitoneal injections of either 500 mg/kg NMN or an equal volume of PBS for 13 days. Where indicated, mice were treated at 8 weeks of age with 25 mg/kg FK866 daily. Mice were sacrificed on day 14, and pancreas was harvested for downstream analysis. For xenograft model, cells (TOV21G: senescent fibroblast = 1:1 at 2 x 10e6 cells) were suspended in 100 uL PBS:Matrigel (1:1) and unilaterally injected subcutaneously into the right dorsal flank of 6-8 week-old female immunocompromised non-obese diabetic/severe combined immunodeficiency (NOD/SCID) gamma (NSG) mice. The mice were administered DOX-containing food following injection of cells. Four days after injection of cells, the mice (n=9 mice/group) were treated with vehicle control, NAM (500 mg/kg; intraperitoneal injection; every other day) for 17 days. NAM was dissolved in water. Tumor size was measured on the indicated days.

Method-specific reporting

n/a	Involved in the study
☐	☒ ChIP-seq
☐	☒ Flow cytometry
☒	☐ Magnetic resonance imaging

ChIP-seq

Data deposition

☒ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☒ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE111841 private token ejaxoaoctngppwb
Files in database submission	HMGA1.RAS.fastq HMGA1.vector.fastq HMGA1_RAS_vs_vector_peaks.txt
Genome browser session (e.g. UCSC)	https://genome.ucsc.edu/cgi-bin/hgTracks?db=hg19&lastVirtModeType=default&lastVirtModeExtraState=&virtModeType=default&virtMode=0&nonVirtPosition=&position=chr7%3A105915638%2D105930638&hgsid=660500681_czyWhekWiOKFcuSNzzJo3dRWqkq9

Methodology

Replicates	HMGA1 CHIP-seq was done for one replicate in RAS and vector condition
Sequencing depth	75bp single end reads: Sample Total_reads Uniquely_aligned HMGA1.RAS 42,177,511 35,433,705 HMGA1.vector 41,669,827 34,146,902
Antibodies	anti-HMGA1 antibody (Abcam, Cat. No. 129153, lot GR211599-2).
Peak calling parameters	HOMER: findPeaks -center -style factor
Data quality	2352 HMGA1.RAS specific peaks with FDR<10% and at least 4 fold over HMGA1.vector control
Software	bowtie, HOMER

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Samples were incubated with 5 uM 2-NBDG (Invitrogen) for two hours, trypsinized and washed with PBS, and run on an LSRII flow cytometer (Becton Dickinson). Analysis was performed using FlowJo Software.
Instrument	FACSCalibur
Software	FlowJo version 7
Cell population abundance	10000 cells were acquired and analyzed
Gating strategy	Forward and side scatter gating strategy was used to eliminate the cell debris, fragments and pyknotic cells. The gated population was analyzed for 2NBDG (FITC) mean fluorescence intensity. Please see an example in Extended Data Figure 3g.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.