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Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the 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
☐	☒ A statement on 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 statistical parameters 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

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	For RNAseq data analysis the tximeta R package (version4.3) (Love et al. 2020) was used to import transcript-level quantification data quantified with Salmon package (Patro et al. 2017). CRISPR–Cas9 screens from the samples were analyzed using software packages MAGeCK and MAGeCKFlute. MAGeCK allows to analyze CRISPR/Cas9 screen data, and performs quality control, read count generation and normalization, calculated beta score to evaluate gene selection performance. MAGeCK's robust rank aggregation (RRA) method was used to identify significantly enriched or depleted CRISPR-screen hits in cells and tumors. MAGeCKFlute R package (Version 4.0.3) was used for data analysis and visualization. CellRanger (v6.0.2), scanpy (v1.7.2) was used For Single Cell Computational analyses. For GSEA was used ClusterProfiler (v3.16.1). For Bulk RNA sequencing data we used RTA (Illumina) for base calling and bcl2fastq2 (v 2.19) for converting BCL to fastq conversion, coupled with adaptor trimming. We performed a pseudoalignment to a kallisto index created from Human transcriptomes GRCh38 using kallisto (0.44.0). No custom algorithms were used in this study.
Data analysis	Prism 9 software was used for statistical analysis. Cellprofilier software was used for quantifying cell proliferation.

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Source data information for main and extended figures is available. Gene expression data that support the findings of this study have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE188391.

Previously published RNA sequencing data that were re-analyzed for the Arriaga cohort under accession number GSE143812 or for MET500 data can be found at this website: https://xenabrowser.net/datapages/?cohort=MET500%20(expression%20centric).

Metabolomics data have been deposited in the Metabolomics Workbench (the NIH Common Fund's National Metabolomics Data Repository (NMDR) website, the Metabolomics Workbench, https://www.metabolomicsworkbench.org where it has been assigned Study ID ST002851. The data can be accessed directly via its Project DOI: http://dx.doi.org/10.21228/M8043D) repository.

All other data supporting the findings of this study are available from the corresponding author upon reasonable request.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	The deidentified DNA and RNA sequencing data are owned by Caris Life Sciences and cannot be publicly shared due to the data usage agreement signed by Dr. Benjamin Izar at Columbia University Iriving Medical Center, New York, NY. Qualified researchers can apply for access to these data by contacting Joanne Xiu, PhD at jxiu@carisls.com, submitting a brief proposal, and signing a data usage agreement.
Recruitment	N/A
Ethics oversight	Human bio specimen research was approved by Columbia University Irving Medical Center Institutional Review Board, #AAAO5706

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	Power analysis was not used to predetermine sample size. Instead sample size was determined based on historical sample sizes that were capable of detecting biologically significant differences in experimental assays. If no historical data was available, pilot experiments were performed. All in vivo experiments were performed with at least 5 biological replicates to ensure reproducibility. Samples sizes for in vivo experiments were chosen based on historical experience and were variable based on numbers of surviving mice available at the end point of the experiments.
Data exclusions	No completed data were excluded from analysis in this manuscript.
Replication	Experiments in this manuscript were reliably reproduced. Experiments were repeated at least two to three times with similar results.
Randomization	Randomization of in vivo experiments was not possible due diet arms involved in the experiment.

Blinding	No blinding was used in these studies due to personnel shortages not allowing for availability of separate investigators for data acquisition and analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Pip4k2c Rabbit Polyclonal antibody (17077-1-AP, Proteintech), 1:1000 Phospho Akt (Ser473) (D9E) XP Rabbit mAb (4060S), 1:1000 Phospho Akt (Thr308) (D25E6) XP® Rabbit mAb (13038S), 1:1000 Phospho p44/42 MAPK (Erk1/2) (Thr202/Tyr204) Antibody (9101S), 1:1000 P44/42 Mapk (Erk1/2) (3A7) Mouse mAb (9107S), 1:1000 Insulin Receptor β (4B8) Rabbit mAb (3025S), 1:1000 Phospho-IGF-I Receptor β (Tyr1135/1136)/Insulin Receptor β (Tyr1150/1151) (19H7) Rabbit mAb (3024s), 1:1000 β-Actin (E4D9Z) Mouse mAb (58169S), 1:2000 For secondary antibodies: Goat Anti-Rabbit IgG Antibody, IRDye® 800CW Conjugated - 0.5 mg (926-32211, LI-COR Biosciences) Goat Anti-Mouse IgG Antibody, IRDye® 680RD Conjugated - 0.5 mg (926-68070, LI-COR Biosciences).
Validation	Western blot antibodies used in this study were extensively used in the literature for previous studies, validation blots are shown in the product information sheets on the Cell Signaling Websites.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	A375, CT26 and HEK293T cells were purchased from ATCC. HCmel12 melanoma cells were kindly provided by Prof. Thomas Tueting (Magdeburg, Germany).
Authentication	the cell lines were not authenticated
Mycoplasma contamination	Cell lines were routinely tested for mycoplasma contamination using Lonza MycoAlert Kit (Cat. # LT07-318).
Commonly misidentified lines (See ICLAC register)	None of the cell lines used in this paper were in the list of misidentified lines.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	All mice were purchased from Jackson Laboratory and/or Charles River. Six to eight-week-old wild-type female C57BL/6J (Charles River, Stock Number: 027), NOD/SCID/IL2gR (Jackson Labs, Stock Number: 005557) and/or BALB/c (Jackson Labs, Stock Number: 000651). Mice received a normal chow diet (PicoLab Rodent 20 5053 laboratory Diet St. Louis, MO) or a ketogenic diet (Thermo-Fisher AIN-76A) where indicated, with free access to drinking water. Animals were housed under the following conditions: 12-12 hour light-dark cycle, 21.1-22.2 C, 30-70% humidity.
Wild animals	No wild animals were used in this study.

Reporting on sex	All mice were female.
Field-collected samples	No field collected samples were used in this study.
Ethics oversight	All animal studies were performed under following IACUC approved animal protocols at Columbia University (AC-AABE6570) and Harvard Medical School (AABQ9616). The maximum subcutaneous tumor size permitted by IACUC at Columbia University and at Harvard Medical School is 20mm. This maximum tumor size was never exceeded in the studies.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A
Study protocol	N/A
Data collection	N/A
Outcomes	N/A

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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	For assessing Cas9 cell cutting efficiency in HCmel12_Cas9 expressing cells, EGFP positive cells were measured using flow cytometry.
Instrument	Data were acquired with FACSCanto flow cytometer (BD Biosciences)
Software	Data were analyzed with FlowJo software (v10 for Mac).
Cell population abundance	Experiments used pure cancer cell line cultures.
Gating strategy	GFP untransduced cells were used to set a negative gate.

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