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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.

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	Oxygen consumption data was collected using Wave 2.4 software. Flow cytometry data was collected using FACS DIVA 8.0.3 software. Metabolite data was collected using Xcalibur 4.1 software. Luminescence values from the tumors were collected using the IVIS 4.5 or the LAGO 2.3.1 imaging systems. Western blot images were collected using Odyssey Fc Imaging System 5.2 From LI-COR.
Data analysis	GraphPad Prism 7.0 and MetaboAnalyst 4.0 were used for statistical tests. Flow cytometry data was analyzed using Flowjo 10.4.2. Metabolite data was analyzed using Tracefinder 4.1 software. Images from tumors were processed using the Living Image 4.5 or the Aura 2.3.1 softwares. Image Studio Lite version 5.0 (LI-COR) was used for the analysis of protein levels.

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. 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

Data from the manuscript are available from the corresponding author on request.

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	All the experiments were performed using sample sizes based on standard protocols in the field. We made an effort to avoid needless use of animals. No statistical test was performed to predetermine sample size. We used statistical analysis consistent with the sample size for each experiment and found sufficient statistical power with the sample sizes utilized in our study.
Data exclusions	For xenograft in vivo experiments, mice were excluded from the analysis if euthanasia had to be applied due to ulcerations or excessive tumor growth prior to the end point of the experiment. This exclusion criteria was pre-established.
Replication	All experimental data was reliably reproduced in multiple independent experiments as indicated in the figure legends. In vivo tumor experiments are from at least two independent cohorts to ensure reproducibility.
Randomization	Experimental animals were not randomized to experimental groups, but were age-matched, sex-matched, and littermates when possible.
Blinding	Investigators were not blinded. In case of leukemia studies blinding was not relevant, as groups consisted of previously genotyped mice in order to have correct experimental and control groups.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Antibodies used for flow cytometry were: anti-Mouse Ter-119 (eBioscience; #48-5921-80; clone TER-119), anti-Mouse NK1.1 (eBioscience; #48-5941-80; clone PK136,), anti-Human/Mouse CD45R (B220) (eBioscience; #48-0452-80; clone RA3-6B2), anti-Mouse CD8a (eBioscience; #48-0081-82; clone 53-6.7), anti-Mouse CD11b (eBioscience; #48-0112-80; clone M1/70,), anti-Mouse Ly-6G (Gr-1) (eBioscience; #48-5931-80; clone RB6-8C5,), anti-Mouse CD4 (Tonbo Biosciences; #75-0041-U100; clone GK1.5). Antibodies used for western blots were: anti-NDUFS2 (Abcam; #ab103024; 1:500 dilution), anti-QPC (Abcam; #ab136679; 1:500 dilution), anti-SDHA (MitoScience; #MS204; clone 2E3GC12FB2AE2; 1:500 dilution), anti-DHODH (Santa Cruz; #sc-166348; clone E-8; 1:500 dilution), anti-FLAG (Sigma; #F1804; clone M2; 1:1000 dilution), anti-GAPDH (Santa Cruz; #sc-32233; clone 6C5, and Sigma; #G9545; 1:2000 dilution), anti-ATP5A (Mitosciences; #MS507; clone 15H4C4; 1:1000 dilution), anti-Tubulin (Cell Signaling; #2144; 1:1000 dilution) and anti-β-Actin (Sigma; # A2228-100UL; clone AC-74,).
Validation	The antibodies used in this study were tested by the manufacturer. Antibodies used for flow citometry: - anti-Mouse Ter-119 (clone number: TER-119 eBioscience; catalogue number: 48-5921-80). This antibody has been used in 25 published figures and can be found in 42 references. The manufacturer also provides antibody testing data. https://www.thermofisher.com/antibody/product/TER-119-Antibody-clone-TER-119-Monoclonal/48-5921-80 - anti-Mouse NK1.1 (clone number: PK136, eBioscience; catalogue number: 48-5941-80). This antibody has been used in 27

published figures and can be found in 28 references. The manufacturer also provides antibody testing data. https://www.thermofisher.com/antibody/product/NK1-1-Antibody-clone-PK136-Monoclonal/48-5941-80

- anti-Human/Mouse CD45R (B220) (clone number: RA3-6B2, eBioscience; catalogue number: 48-0452-80). This antibody has been used in 40 published figures and can be found in 95 references. The manufacturer also provides antibody testing data and advanced verification by relative expression to ensure that the antibody binds to the antigen stated. https://www.thermofisher.com/antibody/product/CD45R-B220-Antibody-clone-RA3-6B2-Monoclonal/48-0452-80

- anti-Mouse CD8a (clone number: 53-6.7, eBioscience, catalogue number: 48-0081-82). This antibody has been used in 40 published figures and can be found in 138 references. The manufacturer also provides antibody testing data. https://www.thermofisher.com/antibody/product/CD8a-Antibody-clone-53-6-7-Monoclonal/48-0081-82

- anti-Mouse CD11b (clone number: M1/70, eBioscience; catalogue number: 48-0112-80). This antibody has been used in 40 published figures and can be found in 230 references. The manufacturer also provides antibody testing data. https://www.thermofisher.com/antibody/product/CD11b-Antibody-clone-M1-70-Monoclonal/48-0112-80

- anti-Mouse Ly-6G (Gr-1) (clone number: RB6-8C5, eBioscience; catalogue number: 48-5931-80). This antibody has been used in 40 published figures and can be found in 102 references. The manufacturer also provides antibody testing data and advanced verification by relative expression to ensure that the antibody binds to the antigen stated. https://www.thermofisher.com/antibody/product/Ly-6G-Ly-6C-Antibody-clone-RB6-8C5-Monoclonal/48-5931-80

- anti-Mouse CD4 (clone number: GK1.5, Tonbo Biosciences; catalogue number: 75-0041-U100). Tonbo Biosciences tests all antibodies by flow cytometry. https://tonbobio.com/products/violetfluor-450-anti-mouse-cd4-gk1-5

Antibodies used for western blots:

- anti-NDUFS2 (Abcam; catalogue number: ab103024; used at a 1:500 dilution). The Abpromise guarantee covers the used of the antibody for WB application. However, the antibody is not available anymore. https://www.abcam.com/ndufs2-antibody-ab103024.html

- anti-QPC (Abcam; catalogue number: ab136679; used at 1:500 dilution). The Abpromise guarantee covers the used of the antibody for WB application. https://www.abcam.com/uqcrq-antibody-ab136679.html#top-294

- anti-SDHA (clone number: 2E3GC12FB2AE2, MitoScience; catalog number: MS204; used at a 1:500 dilution). The Abpromise guarantee covers the used of the antibody for WB application. This antibody has been referenced in 235 publications. https://www.abcam.com/sdha-antibody-2e3gc12fb2ae2-ab14715.html#top-701

- anti-DHODH (clone number: E-8, Santa Cruz; catalog number: sc-166348; used at a 1:500 dilution). This antibody has been referenced in 5 publications. The manufacturer also provides antibody testing data. https://datasheets.scbt.com/sc-166348.pdf

- anti-FLAG (clone number: M2, Sigma; catalog number: F1804; used at a 1:1000 dilution). This antibody has been referenced in 4024 publications. The manufacturer also provides antibody testing data. https://www.sigmaaldrich.com/catalog/product/sigma/f1804?lang=en&region=US

- anti-GAPDH (clone number: 6C5, Santa Cruz; catalog number: sc-32233 and Sigma; catalog number: G9545; used at a 1:2000 dilution). For sc-32233 antibody from Santa Cruz, the antibody has been referenced in 2479 publications. The manufacturer also provides antibody testing data. https://datasheets.scbt.com/sc-32233.pdf. For G9545 from Sigma, the antibody has been referenced in 792 publications. The manufacturer also provides antibody testing data. https://www.sigmaaldrich.com/catalog/product/sigma/g9545?lang=en&region=US

- anti-ATP5A (clone number: 15H4C4, Mitosciences; catalog number: MS507; used at a 1:1000 dilution). The Abpromise guarantee covers the used of the antibody for WB application. The antibody has been referenced in 243 publications. The manufacturer also provides antibody testing data. https://www.abcam.com/atp5a-antibody-15h4c4-mitochondrial-marker-ab14748.html

- anti-Tubulin (Cell Signaling; catalog number: 2144, used at a 1:1000 dilution). This antibody has been referenced in 341 publications. The company tested that The α-Tubulin Antibody detects endogenous levels of total α-tubulin protein, and does not cross-react with recombinant β-tubulin. https://www.cellsignal.com/products/primary-antibodies/a-tubulin-antibody/2144

- anti-β-Actin (clone number: AC-74, Sigma; catalog number: A2228-100UL). This antibody has been referenced in 1412 publications. The manufacturer also provides antibody testing data. https://www.sigmaaldrich.com/catalog/product/sigma/a2228?lang=en&region=US

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	143B-Cytb-WT and 143B-Cytb-Δ cells were previously described (Weinberg et al. PNAS. 2010). Mouse KrasG12D p53-/- (KP) lung tumor cells expressing luciferase were generously provided by Dr. T. Papagiannakopoulos. 293T were from ATCC. Platinum E-retroviral packaging cells were a kind gift from Dr. P. Ntziachristos.
Authentication	Neither of the cell lines used were authenticated.

Mycoplasma contamination	Cell lines tested negative for mycoplasma contamination. Cells were checked periodically.
Commonly misidentified lines (See ICLAC register)	These cell lines are not listed in the database of commonly misidentified cell lines maintained by ICLAC.

Animals and other organisms

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

Laboratory animals	For leukemia experiments we used C57BL/6 Uqcrq (QPC null/wt or QPC null/fx) that have been recently described (Weinberg et al. Nature 2019). Uqcrq (QPC) floxed (Fx), wildtype (WT) and null (-) alleles were genotyped using the following primers: QPC-F: CTTCCGCTCCTCCCGGAAGT, QPC-R: TTCCCAAACTCGCGGCCCATG and QPC-null: CAATTCCAGCCAACAGTCCC. Ubc-CreERT2 mice were obtained from the Jackson Laboratory. Wild-type C57Bl/6 were used as recipients for T-ALL experiments. 8 to 12 weeks old mice of both sexes were used for experiments. For xenograft tumor studies, we used male J:Nu mice (8 to 12 weeks) obtained from Jackson Laboratory. For the orthotopic lung tumor model, we used male C57BL/6 mice (8 to 12 weeks).
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the field.
Ethics oversight	All mouse work was done in accordance with Northwestern University Institutional Animal Care and Use Committee (IACUC).

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

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	Sample preparation is described in detail in the methods section of the manuscript. Briefly, for T-ALL experiments, lineage (CD4, CD8a, B220, CD11b, Gr-1, NK1.1, Ter-119)-negative, and GFP+ bone marrow cells transduced with the Notch1ΔE-GFP retrovirus were sorted on BD FACS Aria systems. To asses tumor burden, spleen, and one set of pelvis, femur, and tibia were harvested from each recipient, and analyzed for the number and % of GFP+ T-ALL cells, using PKH reference microbeads (Sigma). Samples were harvested from adult mice. To obtain a single-cell suspension, tissues were disrupted using scored 60mm petri dishes in PBS containing 2% FBS and filtered through a 70µM nylon mesh filter. Expression of GFP was analyzed using BD FACSymphony. For in vitro proliferation experiments, supernatant containing dead cells and cells attached to the wells were collected and centrifuged at 300 × g for 5 min. AccuCount Fluorescent Particles from Spherotech were added to count the cells. Cell viability was assessed by DAPI staining. Numerical values for number of cells or percentage with statistics for each graph is provided in Source Data files.
Instrument	BD LSR Fortessa, BD FACSymphony or BD FACSAria cell sorter.
Software	BD FASC Diva was used for collection of the data. All data was analyzed using FlowJo software.
Cell population abundance	The cells were periodically sorted to maintain high protein expressions. An aliquot of the sorted cells were always collected and run on a cytometer to verify purity of the samples collected. In addition, cell counts were performed on samples post sort to verify correct cell numbers.
Gating strategy	A supplemental figure is provided to show the gating strategy for T-ALL burden analysis. 2 different analysis were done: # of GFP+ Cells: Used the following flow plots to obtain: SSC-A vs. FSC-A: count of Lymphocytes --> A FSC-H vs. PE-A: count of PKH beads --> B APC-Cy7-A vs. BB515-A (showing the Lymphocytes population): % of GFP+ and Live lymphocytes --> C Actual # of lymphocytes = (A / B) x PKH bead concentration (in beads/ml, counted using hemocytometer each time) x total volume of cell suspension (ml) # of GFP+ cells = Actual # of lymphocytes x C

% of GFP+ Cells:
SSC-A vs. FSC-A: Lymphocytes population
FSC-H vs. FSC-A (showing the Lymphocytes population): Singlet population
SSC-H vs. APC-Cy7-A (showing the Singlet population): Live population
SSC-H vs. BB515-A (showing the live population): % of GFP+ population --> D
% GFP+ Cells = D

For proliferation experiments, beads and cells were identified first by discrimination by size (FSC-A by SSC-A). Singlets were then distinguished using FSC-A by FSH-H. Beads and Live cells were further gated by the appropiate fluorochrome used.

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