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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.

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	MS - XCalibur, CellTiterGlo - SoftMaxPro 7.0.3, microscopy images - ZEN2 (by ZEISS), histology images - cellSensStandard, qPCR - QuantStudio v1.3, mice in vivo imaging - IVIS Lumina.
Data analysis	Excel, Prism version 7.0b, R, FlowJo (version 10.3), ChemDraw (Perkin Elmer, Waltham, MA), CFM:ID (cfmid.wishartlab.com), METLIN (www.metlin.scripps.edu), Sirius (version 3.5.1; University of Jena, Germany), ImageJ

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 authors declare that all data generated or analyzed during this study are included in this published version and its supplementary information files. Extended Data Figures 1, 2, 3, 4 and 5, as well as Source Data for Figures 1, 2, 3, 4 and 5 are provided with the online version of the paper.

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 ☐ Ecological, evolutionary & environmental 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	Sample size was determined by the nature of the experiment: Experiments in culture were repeated at least twice, and were done for the most part on more than one cell line (with exceptions such as the co-culture of 42 barcoded hematopoietic cell lines and the CRISPR/Cas9-based screen, that was done twice but in one cell line). This sample size was determined based on our desire to test the reproducibility of our results in different cell lines and not just as an identical replicate. Mice experiments were done with 6 mice per group. However, some mice had to be euthanized prior to the experiment end point and therefor the total number for some of the final assays ended up less than 6 but never less than 4. This sample size was determined by our experience with in vivo experiments and the minimum number of mice commonly required for significant results. Patients groups were at least 18 patients per analyzed group. This number was determined by data availability.
Data exclusions	No mice were excluded once incorporated into the experiment and treated. No patients were excluded from the analysis of the expression data and survival presented in figure 3. Data exclusions due to technical issues was done in these instances: 1. One cell line was excluded from the co-culture final analysis because it was underrepresented in the initial time point (the barcode read number appeared very different from the rest of the cell lines in the experiment). 2. A single technical replicate was sometimes excluded if was clearly an out-lier and was one of 3 replicates in qPCR, LC/MS, or survival assays. 3. sgRNAs with less than 40 reads total in the final CRISPR/Cas9-based screen.
Replication	For cell culture experiments, full biological replicates were done for all experiments, and often done in more than one cell line. Technical triplicates within each biological replicate were done for qPCR, LC/MS, survival assays, and cell counting. No attempts for replication were excluded unless failed due to low transduction rate. HEL cells became sensitive following transduction with sgRNAs targeting FTCD and puromycin selection and were discarded if high death rate was observed. The experiment described in figure 4 initially included 6 mice in each group but 3 mice had to be euthanized before the rest: 1 mouse from the vehicle-treated group. 2 mice from the histidine supplementation group.
Randomization	This question is relevant only for the in vivo experiment presented in figure 4 and 5 because only these experiments involved animals that had to be put in different cohorts. Other experiments included cells with different genotypes so no randomization was possible. In the in vivo experiments 50 mice were initially injected with HEL cells. However, only mice that clearly showed tumors were taken for tumor size evaluation by luciferase imaging. Of the tumor-bearing mice, mice with tumors that were too big (> 0.5 cm apparent tumor) were excluded and euthanized due to humane conduct of research. Of the remaining mice, 24 or 26 mice with similar sized tumors (evaluated by luciferase imaging in vivo) were randomly divided into the 4 treatment groups. The randomized selection was done by picking unlabeled mouse from a large cage that contained all relevant mice and placing in one of the experimental cages.
Blinding	Survival assay - methotrexate was dispensed into wells with cells expressing different plasmids by an automatic compound printer. Output was read by a plate reader so no blinding was necessary. Cell counts - flasks were labeled, but counting was done using an automated coulter counter. LC/MS - peak selection and data analysis were done blindly by the metabolic profiling core facility staff. Sample names were added to the output excel file at the conclusion of the analysis.

Patients expression data - the data were collected by the COG group prior to any analysis applied by the authors.

Mouse experiments - mice selection for the experiment was done based on similar tumor size (24 or 26 total mice), then individual mice were blindly selected for each of the 4 experimental groups. H&E slides were blindly separated into 2 groups by two lab members: both lab members were asked to grade the tumors by their general appearance and necrotic state and both graded the tumors from mice treated with methotrexate and histidine supplementation as the most necrotic and separated them from all other tumors. However, necrotic areas margins were selected by N.K. in a non-blinded process.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☒	☐ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials: Unique reagents include plasmids constructed for this manuscript. These are readily available for the usage of the scientific community through AddGene. All other materials and reagents are not unique for this study.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s):
SKM1, P12-Ichikawa, MOLT4, PF382, SEMK2 - Thomas Look (DFCI)
SUDHL4, HBL1, LY7, U2932 - Margaret A. Shipp (DFCI)
EOL-1, CEM, REH - Scott A. Armstrong (DFCI)
KU812, NOMO1, K562, HEL - Jim Griffin (DFCI)
697, NALM6 - David M. Weinstock (DFCI)
SUDHL8, LY8 - Anthony G. Letai (DFCI)
NCIH1666 - Professor Doug Lauffenburger (MIT)
Mono Mac 6 - Dr. Marina Zaitseva (FDA)
WSU-DLCL2 - Professor Ayad M. Al-Katib (Wayne State University School of Medicine)
CH-157 MN - Professor Randy Jensen (University of Utah)

All other cell lines were in the Sabatini lab's cell bank and were collected or purchased by former lab members.

Authentication:
STR verification was performed for all cell lines used in the study.
The cell lines below were tested after the initial co-culture experiment and were excluded from follow-up work due to possible small contamination found by STR analysis:
SKM1
MOLT16
HT
RS411
LY7
SUDHL8
HL-60

Mycoplasma contamination: Cell lines were tested for mycoplasma contamination when first thawed, and routinely every month or two. All cells were found negative for mycoplasma in all tests.

Commonly misidentified lines (See ICLAC register): No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	NOD-SCID mice - NOD.CB17-Prkdcscid/NCrCrl (originally purchased from Charles River and maintained at the Whitehead mouse facility by self breeding). HEL cell-derived tumors experiment - 24 females. Ages 8-11.5 weeks. Mean 10.7 weeks. SEM cell-derived tumors experiment - 26 females. Ages 12-18 weeks. Mean 14 weeks. HEL cell-derived tumors long term experiment - mice 1-22 females. mice 23-31 males. Ages 6-10 weeks. Mean 10 weeks.
Wild animals	na
Field-collected samples	na