nature research

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Last updated by author(s): Jan 18, 2019

Reporting Summary

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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	Cell death was recorded with the Countess II(Life Technologies); Becton Dickinson FACSCalibur machine was used to collect flow cytometry data. ALOX12 and GPX4 enzymatic activity assay and Glutathione levels were recorded with a 96-wells plate reader (BIO-Tek Instruments, INC).
Data analysis	Data quantification were performed with Excel, Image J and CellQuest and statistical analysis with Excel and GraphPad Prism V6. Images were processed with Adobe Photoshop.

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

The ALOX12 gene expression data for normal versus cancer human tissues were derived from Oncomine database(https://www.oncomine.org/resource/). Source data for Figs. 1a,c,f, 2a-b, d-e,g, 3c-d,h, 4b-c,f, 5d-f,h-i, 6b-d,f-h, 7c-e and 8a-g and Supplementary Figs. 1b,d-e, 2b, 3b-d, 5c-d, 6j,7a-c and 8d have been provided as Supplementary Table 1. All other data supporting the findings of this study are available from the corresponding author on reasonable 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	The sample size was determined based on our experiments. For animal experiment (survival curve in Fig. 3d) has at least n=6 independent mice per group. Unless explicitly stated, 3 independent experiments were performed to achieve Student's t-test analysis.
Data exclusions	No data was excluded from the study.
Replication	Figs. 1b,d-e,g, 2c,f, 3a,g, 4c(bottom panel), d-e, 5a-c,f(right panel),g, 6a,e, 7a-b, d(right panel),e(right panel) and Supplementary Figs. 1c, 3a,e, 4a-c, 6a-f,h-i, 8b-c were independently repeated twice. All the other experiments were independently repeated at least three times.
Randomization	6-8 week female nude mice were chosen as xenograft models, and randomly allocated into experimental groups.
Blinding	For in vitro cell-based experiments, the investigators were not blinded during data acquisition and analysis. The application of treatments and processing procedures made it difficult for blinding but there was no human bias given all the data were collected independently using instrumentation. For the animal experiments the investigators were not blinded to the group allocation. However, at least two observers measured xenograft tumor volumes/weights or the latency of tumor formation/survival time to alleviate human bias in these data.

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	rimary antibodies specific for p53 (DO-1) (SC-126 ; Santa Cruz;1:1000 dilution), p53 (FL-393) (SC-6243 ; Santa Cruz;1:1000 dilution), MDM2 (Ab-5) Mouse mAb (4B2C1.11)(OP-145; Millipore; 1:100 dilution), p21 (SX118) (sc-53870; Santa Cruz; 1:1000 dilution), MDMX (A300-287A; Bethyl; 1:1000 dilution), p19-ARF antibody (5C-3) (ab-26696; Abcam; 1:1000 dilution), PUMA antibody(H-136) (sc-28226; Santa Cruz; 1:500 dilution), SLC7A11 antibody (D2M7A) (12691s; Cell Signaling; 1:500 dilution), ACSL4 antibody (A5) (sc-271800; Santa Cruz; 1:1000 dilution), V5 (R960-25; Invitrogen; 1:1000 dilution), HA (11867423001; Sigma; 1:1000 dilution), ALOX12 antibody (C-5) (sc-365194; Santa Cruz; 1:200 dilution), ALOX15 (ab-80221; Abcam; 1:1000 dilution) and vinculin (V9264; Sigma-Aldrich; 1:5000 dilution). The more detailed information is provided in the Supplementary Table 3.

Validation	All antibodies used were validated by the respective commercial source for the application used .
	p53(DO-1), https://www.scbt.com/scbt/product/p53-antibody-do-1;
	p53(FL-393), https://www.scbt.com/scbt/product/p53-antibody-fl-393;
	MDM2, http://www.emdmillipore.com/US/en/product/Anti-MDM2-Ab-5-Mouse-mAb-4B2C1.11,EMD_BIO-OP145;
	p21, https://www.scbt.com/scbt/product/p21-antibody-sx118;
	MDMX, https://www.bethyl.com/product/A300-287A/HdmX+MDM4+Antibody;
	p19-ARF, https://www.abcam.com/cdkn2ap19arf-antibody-5-c3-ab26696.html;
	PUMA, https://www.scbt.com/scbt/product/pumaalpha-beta-antibody-h-136;
	SLC7A11, https://www.cellsignal.com/products/primary-antibodies/xct-slc7a11-d2m7a-rabbit-mab/12691;
	ACSL4, https://www.scbt.com/scbt/product/acsl4-antibody-a-5;
	V5, https://www.thermofisher.com/antibody/product/V5-Tag-Antibody-Monoclonal/R960-25;
	HA, https://www.sigmaaldrich.com/catalog/product/roche/roahaha?lang=en&region=US;

ALOX12, https://www.scbt.com/scbt/product/12-lo-antibody-c-5;
ALOX15,https://www.abcam.com/15-lipoxygenase-1-antibody-ab80221.html;
vinculin, https://www.sigmaaldrich.com/catalog/product/sigma/v9264?lang=en&region=US.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	U2OS, H1299, A549, A375, MCF7, HCT116, HT1080, H460 and SJSA cancer lines were obtained from American Type Culture Collection (ATCC) and have been proven to be negative for mycoplasma contamination. Mouse embryonic fibroblasts (MEFs) were generated from day 13.5 embryos.
Authentication	The cell lines were not authenticated.
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination.
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.

Animals and other organisms

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

Laboratory animals	Eμ-Myc, Trp53+/- and ALOX12-/- mice with both male and female for breeding at 6-8 weeks were ordered from Jackson Laboratories. Eμ-myc , Eμ-myc; ALOX12+/- , and Eμ-myc; p53+/- with both gender from 1-12 months of age were used to determine tumorigenesis and survival rate. For ACSL4-/- mice, gene targeting of mouse ACSL4 gene was designed to flank the second coding exon (exon 2) with loxP sites (flox) to generate a conditional knockout allele of ACSL4. The cre mediated deletion of exon 2 causes translational reading frame shift and truncation of the rest of the ACSL4 protein. The ACSL4 conditional knockout mice were maintained on a mixed background of 129Sv and C57BL/6J through breeding between littermates. NU/J nude female mice at 6-8 week old purchased from Charles River were used for xenograft model.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	The study is compliant with all relevant ethical regulations for animal experiments. All the experimental protocols were approved by the Institutional Animal Care and Use Committee of Columbia University.

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	The cells were incubated with medium containing 5uM of BODIPY-C11 dye and the cells were returned to the cell culture incubator for 20 min. Cells were harvested and washed two times with PBS followed by re-suspending in 500ul of PBS.
Instrument	Becton Dickinson FACSCalibur machine
Software	using CellQuest to collect data
Cell population abundance	10,000 cells were analyzed for each sample
Gating strategy	The starting cell population gating by Forward Scatter and Side Scatter was used to make sure doublet exclusion. Only single cell was used for analysis.

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