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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 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	Living Image 4.5. BD FACSDiva. Zeiss Zen 2. SoftMax Pro 7. Leica Application Suite.
Data analysis	Origin Lab Pro 2020. Graphpad Prism 8. ImageJ. R. Living Image 4.5. FlowJo V10. Bitplane Imaris 9. Zeiss Zen 2. Pannoramic Viewer 1.15. UCSF Chimera 1.11. Microsoft Excel 2016, Customized R codes (available at https://github.com/wangtaifr/Kircher2020).

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 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 main data supporting the results in this study are available within the paper and its Supplementary Information. The raw and analysed datasets generated during the study are too large to be publicly shared, yet they are available for research purposes from the corresponding authors 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	No statistical method was applied to predetermine sample size. Sample sizes in the study were chosen to comply with local animal-ethics policies and financial constraints, to use the smallest possible number of animals to obtain data. They are all commensurate with traditions in the field.
Data exclusions	No data were excluded.
Replication	Experimental findings were reproduced. All attempts at replication were successful.
Randomization	Mice were randomly assigned into groups, grafted with tumors, allocated for treatments or used for toxicity, pharmacokinetic and biodistribution studies. No other randomizations were performed.
Blinding	No blinding was performed.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	anti-EEA1 (ab2900, Abcam, 0.8 µg/mL); anti-LAMP1 (1D4B, DSHB, 0.5 µg/mL); biotinylated goat anti-rabbit and goat anti-rat IgG (BA-1000 and BA-9401, Vector Labs,1:200 dilution); anti-Iba1 antibody (019-19741, Wako, 0.5 µg/mL); anti-β-actin (A1978, Sigma-Aldrich,1:5000 dilution); anti-p-Akt (Ser473)(9271, Cell Signaling, 1:1000 dilution); anti-Akt (9272, Cell Signaling, 1:500 dilution); anti-p-c-raf (Ser259)(9421, Cell Signaling, 1:1000 dilution); anti-p-MEK1/2(Ser217/221)(9154, Cell Signaling, 1:500 dilution);anti-p-ERK1/2(Thr202/Tyr204)(4370, Cell Signaling, 1:1000 dilution); anti-ERK1/2(9102, Cell Signaling, 1:1000 dilution); anti-c-myc (SC-764, Santa Cruz Biotechnologies, 1:500 dilution); anti-p-S6 (Ser235/236)(4858, Cell Signaling, 1:2000 dilution); anti-RIP1 Kinase (4926, Cell Signaling, 1:1000 dilution); anti-Bid (8762, Cell Signaling, 1:1000 dilution).
Validation	Antibodies were validated for western blot, immunofluorescence or immunohistochemistry.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cell lines in the study were acquired from the American Type Culture Collection (ATCC), including MDA-MB-231, BxPC-3, MDA-MB-468, 4T1, B16-F10 and LLC. MC-38 was acquired from the Cell Bank of the Chinese Academy of Sciences.
Authentication	No further authentication was performed.
Mycoplasma contamination	All cell lines used in the study tested negative of mycoplasma contamination.

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	All mice used in the study were female and acquired from the Jackson Laboratory (JAX). J:NU (Foxn1nu/Foxn1nu), BALB/cJ and NSG (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) mice were used. Mice undergoing experimental procedures were 8–16 weeks old, depending on tumor-growth rates, and weighed 0.020–0.025 kg.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal procedures were approved by the Institutional Animal Care and Use Committees (IACUC) at Memorial Sloan Kettering Cancer Center, following NIH guidelines.

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	For apoptosis and necrosis staining, harvested cells were resuspended in binding buffer. CF488-Annexin V and EthD-III were added, followed by incubation at room temperature for 15 min away from light on a rotator and analyzed by flow cytometry. For cell-cycle analysis, harvested cells were fixed in drop-wise added ice-old 70% ethanol for 4 hrs at 4°C. After further washes with PBS, cells were stained with PI/RNase staining buffer (BD PharmingenTM) at room temperature for 30 min and immediately analysed by flow cytometry. For JC-1 assay, JC-1 was freshly prepared by diluting 1:10 v/v in 37°C culture medium, added to each well at a volumetric ratio of 1:10 to medium and incubated at 37°C for 30 min. Cells were harvested, washed twice with PBS and resuspended in JC-1 assay buffer for flow-cytometric analysis. Please refer to Methods for further details.
Instrument	BD LSR II (BD Biosciences)
Software	BD FACSDiva was used for collection, and FlowJo V10 was used for analysis.
Cell population abundance	No cell sorting was performed.
Gating strategy	Cells were gated on FSC/SSC-area and width.

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