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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	RT-PCR data were acquired with QuantStudio 6 Flex Software 1.3. Confocal images were acquired with Leica LASX (Leica SP8 or Leica Stellaris) or ZEN 2 (Zeiss LSN700) softwares. Western blotting was acquired with LAS4000 ImageQuant 1.2. LSRFortessa X20 cell analyzer (BD) for cytometer analysis. Microarrays with NextSeq500 Illumina BBDuk (BBMap v. 37.87) proprietary software with parameters indicated in the Lexogen data analysis protocol. TSA-based Opal method (Akoya Biosciences) on the Leica BOND RX automated immunostainer (Leica Microsystems) was used for Multiplex Immunofluorescence. Elettron microscopy images were acquired with a Tecnai G2 (FEI) transmission electron microscope operating at 100kV and captured with a Veleta (Olympus Soft Imaging System) digital camera. Oxygen consumption was measured using the Seahorse XF24 (Seahorse Bioscience).
Data analysis	Data were analyzed with Microsoft Excel 16.16.22 or Prism 9. Gene list enrichment analysis was performed with Enrichr (http://amp.pharm.mssm.edu/Enrichr/). Heatmaps with Heatmapper (http://www.heatmapper.ca/). MultiQuant™ software version 3.0.2 was used for metabolite data analysis and peak review of chromatograms. Multiplex stained slides were imaged using the Mantra Quantitative Pathology Workstation (Akoya Biosciences) at 20X magnification. Images were treated (crop, overlay, colors) with ImageJ according to NPG's image integrity rules. Microarray data were treated in R (version 3.0.2) using Bioconductor libraries (BioC 2.13) and R statistical packages. After trimming, reads were aligned to the Mus musculus genome (GRCm38.p6) using STAR (v. 2.7.6a). The gene expression levels were quantified using featureCounts (v. 2.0.1). Genes were sorted removing those that had a total number of counts below 10 in at least 3 samples. All RNA-seq analyses were carried out in the R environment (v. 4.0.0) with Bioconductor (v. 3.7). We computed differential expression analysis using the DESeq2 R package (v. 1.28.1). Normalization to CPM has been performed exploiting the cpm function from the edgeR package (v. 3.32.0).

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

Metabolomics and targeted lipidomics data have been deposited (Figshare database 10.6084/m9.figshare.7338764). RNAsequencing have been deposited in GEO GSE189803.

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	Sample size was determined based on previous experience and on the pertinent literature indicated in the text.
Data exclusions	No data was excluded from analysis.
Replication	Every experiment was independently repeated at least twice with multiple independent biological replicates, in at least two different cell lines. The unique exception is metabolomics, which was performed as a single experiment with at leasdt n=4 independent biological replicates for each condition. All attempts at repetition were successful. Key data were replicated by different operators.
Randomization	Allocation of mice to injection of the different cell lines and to treatment was random. We chose to perform all other experiments without randomization because knowledge of the samples' identity cannot influence the measured outcomes.
Blinding	This is not relevant to our study, as subjective rating of data was not involved. Results involved equipment-based quantitative measurements rather human-based evaluation or classification.

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

Primary antibodies (catalogue number; validation) were: 8OH(d)G (1:300, SCBT sc-66036; IF signal increases in cells treated with Cumene, cytoplasmic but not nuclear signals decreases in cells treated with RNAse); 4HNE (1:100, ABCAM ab48506; IF signal increases in cells treated with Cumene); NRF2 PS40 (1:2000, ABCAM ab76026; IF nuclear signal intensity increases in cells with inhibited KEAP1); DRP1 (1:200, BD 611738; punctated IF staining co-localizing with mitochondrial markers and disappearing upon Drpitor1a treatment); FLAG mouse monoclonal (1:200, Sigma M2; IF in cells with/without transfected FLAG-tagged proteins); FLAG rabbit monoclonal (1:1000, CST BK14793;IF in cells with/without transfected FLAG-tagged proteins); Alexa647-Phalloidin (1:500, Thermo A22287; detects filamentous cytoplasmic structures that are lost upon treatment of cells with latrunculinA); TOMM20 (1:400, Thermo STD4-72; IF signal co-localizes with other mitochondrial markers); Cleaved Caspase-3 (1:500, CST 9661S; IF signal detected only upon cell-death inducing stimuli); GFP (1:300, Abcam AB13970; IF signal detected only in GFP-expressing cells); CD31

(1:100, Optistain DIA310); Collagen-I (1:2000, Abcam AB34710); KEAP1 used for WB and PLA (1:300, STCB sc-365626; IF and WB signal fades with NRF2 siRNAs); NRF2 used for WB (1:1000, Proteintech 13396-1-AP; WB signal disappears with NRF2 siRNAs); NRF2 used for PLA (1:500, CST 12712; IF and WB signal fades with NRF2 siRNAs); DRP1p616 for IF and WB (1:100 IF, 1:500 WB, CST#4494); DRP1p637 for WB (1:1000, CST #4867).
Secondary antibodies were: Alexa-488 anti-mouse (1:1000, Thermo A21202); Alexa-568 anti-rabbit (1:1000, Thermo A11036); Alexa-568 anti-mouse IgG1 (1:1000, Thermo A21124); Alexa-647 anti-mouse IgG2b (1:1000, A21242). HRP-rabbit (1:1000, SIGMA A0545), HRP-mouse (1:5000, GE-HEALTHCARE RPN4201V).

Validation

All antibodies chosen for this work have been previously used and validated in literature and by manufacturers. Antibodies were used following manufacturers guidelines and were further validated in our laboratory by using relevant controls or, when possible, independent techniques. Primary antibodies (catalogue number; validation) were: 8OH(d)G (1:300, SCBT sc-66036; IF signal increases in cells treated with Cumene, cytoplasmic but not nuclear signals decreases in cells treated with RNAse); 4HNE (1:100, ABCAM ab48506; IF signal increases in cells treated with Cumene); NRF2 PS40 (1:2000, ABCAM ab76026; IF nuclear signal intensity increases in cells with inhibited KEAP1); DRP1 (1:200, BD 611738; punctated IF staining co-localizing with mitochondrial markers and disappearing upon Drpitor1a treatment); FLAG mouse monoclonal (1:200, Sigma M2; IF in cells with/without transfected FLAG-tagged proteins); FLAG rabbit monoclonal (1:1000, CST BK14793;IF in cells with/without transfected FLAG-tagged proteins); Alexa647-Phalloidin (1:500, Thermo A22287; detects filamentous cytoplasmic structures that are lost upon treatment of cells with latrunculinA); TOMM20 (1:400, Thermo STD4-72; IF signal co-localizes with other mitochondrial markers); Cleaved Caspase-3 (1:500, CST 9661S; IF signal detected only upon cell-death inducing stimuli); GFP (1:300, Abcam AB13970; IF signal detected only in GFP-expressing cells); CD31 (1:100, Optistain DIA310); Collagen-I (1:2000, Abcam AB34710); KEAP1 used for WB and PLA (1:300, STCB sc-365626; IF and WB signal fades with NRF2 siRNAs); NRF2 used for WB (1:1000, Proteintech 13396-1-AP; WB signal disappears with NRF2 siRNAs); NRF2 used for PLA (1:500, CST 12712; IF and WB signal fades with NRF2 siRNAs); DRP1p616 for IF and WB (1:100 IF, 1:500 WB, CST#4494); DRP1p637 for WB (1:1000, CST #4867).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

MCF10A and MCF10A-RAS cells were obtained from S. Santner. D2.0R cells wwre obtained from M. Montagner.

Authentication

MCF10A-RAS cells were STR verified as MCF10A derivatives, and further authenticated based on exon PCR sequencing to identify coding point mutations present in MCF10AneoT (MAP3K12 A662D), MCF10AT1 (also known as MCF10AT1k, or MCF1oA MII - PCSK5 M452I) and MCF10CA1a cells (also known as MCF10A MIV - PCSK5 M452I and PIK3CA H1047R). D2.0R are syngeneic to BALB/C mice, thus excluding STR profiling, and were authenticated based on differential behavior compared to another more aggressive isogenic cell line, D2.A1 (see Montagner et al., NCB 2020).

Mycoplasma contamination

All cell lines were routinely tested negative for Mycoplasma contamination by the ATCC Mycoplasma Contamination Detection PCR Kit and by DAPI staining.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines.

Animals and other organisms

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

Laboratory animals

Mus musculus, BALB/C strain, females, 6-8 weeks. Mus musculus, CD1 strain, males, 6 months.

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve samples collected from the field.

Ethics oversight

Animal experiments were performed according to Italian laws, as approved by the University Animal Welfare Commission (OPBA) and authorized by the Ministry of Health (615-2020-PR) for lung and mammary breast cancer assays. Animal studies were approved by the University College London Biological Services Ethical Review Committee and licensed under the Animals (Scientific Procedures) Act 1986 (Home Office, London, United Kingdom) for normal lung decellularized ECM scaffolds. The bleomycin model were performed under the UK Home Office Animal Research project license P36565407.

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	Staining for ROS and FITC-cystine uptake were carried out by incubating cells in plate at the end of the experiments with the indicated reagents in full medium w/out phenol red (DCFDA 1 microM 10 min, MitoSOX 1 microM 10 min, C11-Bodipy-581/591 5 microM 15 min, FITC-cystine 5 microM 30 min). After trypsinization and a brief wash in 1xHBSS, quantification was run on live cells in 1xHBSS (Ca- and Mg-free). For detection of stably-expressed Grx1-roGFP2 sensor fluorescence ratio, cells were fixed after trypsinization with 4% PFA at 4°C for 7 min. Analysis was carried out on a LSRFortessa X20 cell analyzer (BD). Cells were gated based on SSC-A or FSC-A to eliminate cell debris, and on SSC-W to eliminate cell doublets. DCFDA and FITC-cystine were measured using a FITC-A filter. MitoSOX with a PE-A filter. The MFI (median fluorescence intensity) was measured for each independent biological sample, based on at least 3*104 gated events. For C11-BODIPY-581/591 the signals from both non-oxidized C11 (PE-TexasRed) and oxidized C11 (FITC-A) were acquired, and the ratio of FITC-A to PE-TexasRed was calculated for each sample. For Grx1-roGFP, the signals from both non-oxidized (FITC-A) and oxidized (BV510-A) were acquired, and the ratio of BV510-A to FITC-A was calculated for each sample.
Instrument	LSRFortessa X20 cell analyzer (BD)
Software	BD FACSDiva 9.0
Cell population abundance	Flow cytometry was used to quantify fluorescence in whole live single-cell populations, by using at least 30000 cells in the final gate for each biological replicate. The number or percentage of cells has not been used as an experimental parameter, because only the median fluorescence intensity was considered.
Gating strategy	Cells were gated on SSC-A and FSC_A to select the primary population; on SSC-W and SSC-A to eliminate cell doublets. Subsequent gating startegies for each probe or stain are provided in the Extended Data Figures.

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