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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	No software was used for data collection.
Data analysis	The R (version 3.4.4) packages "edgeR" and "DESeq2" were used to normalize and calculate differentially expressed genes. The results were then plotted using "heatmap.2" from the R packages "gplots" and "ComplexHeatmap". The edgeR likelihood ratio (LR) was used to generate a pre-ranked gene list for Gene Set Enrichment Analysis. GSEA was then run pre-ranked with default parameters (1000 gene set permutations, weighted enrichment statistic), using the Hallmarks, Biocarta, and REACTOME gene set collections provided by MSigDB (http://software.broadinstitute.org/gsea/msigdb). Lipidomics heatmaps were generated with in R (version 3.6.1) using the pheatmap package (version 1.0.12). Microarray dataset GSE14020 was downloaded from Gene Expression Omnibus and collected using the Affymetrix Human Genome U133/A Array platforms. The raw data was converted to a recognizable format by GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/). GEO2R performs comparisons on original submitter-supplied processed data tables using the GEOquery package (version 2.40.0)which parses GEO data into R data structures that can be used by other R packages (version 3.2.3) and limma (Linear Models for Microarray Analysis, version 3.26.8) R package from the Bioconductor project. After log2 transformation and normalization, a Fisher's exact test was used to assess statistical significance of FASN or SCD expression between metastatic brain tissue samples and samples from other metastatic tissues (bone, lung, and liver).

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

Raw count data (.txt file) from RNA sequencing of patients with matched primary breast and metastatic tumors were downloaded from hhttps://github.com/npriedig/jnci_2018 (reference #29).

The metabolomics and lipidomics datasets generated for main figures (1a, 4c-f) and extended data figures (5e,f and 7a,b) are provided in extended data tables 1 and 3. All raw data used for statistical analyses (Fig1b; Fig. 3a,b&e; Fig.4c-f,h,l&j; ExtDataFig. 2b,c&n; ExtDataFig 4a,b,c&f; ExtDataFig 5c-f; ExtDataFig. 6c,d; ExtDataFig. 10b-f&h-j) are provided in a Source Data File.

Gene array datasets (human[GSE14020] and mouse model [GEO accession number:GSE86849]) analyzed are publicly available and previously published.

Remaining datasets generated during and/or analyzed in the current study are available form 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 number of mice required to demonstrate statistical significance in each group was estimated based on findings from previous experiments (reference #6). No statistical method was used to predetermine sample size.
Data exclusions	No data were excluded
Replication	All attempts at replication were successful.
Randomization	Tumor-bearing mice (figure 4 i,j) were randomly allocated to control or treatment group.
Blinding	Experimenters were not blinded during data collection.

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-FASN (1:1000 for WB, 1:200 for IHC; Cell Signaling Technology, 3180S), anti-ACC1 (1:1000; Cell Signaling Technology, 4190S), anti-ACLY (1:1000; Cell Signaling Technology, 13390S), anti-SCD1 (1:1000; Abcam, ab19862), anti-beta-actin (1:5000; Cell Signaling Technology, 8457S), anti-Iba1 (WAKO, 019-19741, 1:2000 dilution), anti-HER2 (Cell Signaling Technology, 2165, 1:200 dilution), anti-SMA (MilliporeSigma, C6198, 1:100), anti-GFAP (DAKO, M0761, 1:50).

For WB, anti-rabbit IgG, HRP-linked antibody (Cell Signaling Technology, 7074) or anti-mouse IgG, HRP-linked Antibody (Cell Signaling Technology, #7076) were used at 1:5000).

For immunohistochemistry, epitopes were detected by DAB Chromagen substrate (Dako, K346811-2) or with an Cyanine3 (anti-rabbit; Jackson ImmunoResearch, 711-165-152 | anti-mouse; Jackson ImmunoResearch, 711-165-151) or Cyanine5 fluorescence-conjugated secondary antibodies (anti-rabbit; Jackson ImmunoResearch, 711-175-152 | anti-mouse; Jackson ImmunoResearch, 711-165-150).

Validation

All antibodies have been validated by vendor (CST) and our own data provides positive and negative controls.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

BT474 and MDAMB361 cell lines were purchased from ATCC. JIMT1 cells were from the laboratory of Todd Golub lab (Jin X et al. 2020, Nature)

Authentication

Cell lines were authenticated (Cell Check)

Mycoplasma contamination

We confirm that all cell lines tested negative for mycoplasma (Mycoalert Plus Mycoplasma Detection kit, Lonza, LT07-710)

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified lines were used in the study.

Animals and other organisms

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

Laboratory animals

This study utilized Nude and NSG female mice (8-12 weeks old at tumor implantation). During the experimental period, all mice were housed in microisolator cages, and maintained in our Cox-7 defined-flora animal facility. All the animal rooms inside the facility were kept at the temperatures about 64-79 oF and the range of relative 30-70% humidity, with a 12-hour light/dark cycles.

Wild animals

No wild animals were used in the study.

Field-collected samples

No filed collected samples were used in the study.

Ethics oversight

All animal procedures were performed according to the guidelines of the Public Health Service Policy on Human Care of Laboratory Animals and in accordance with a protocol approved by the Institutional Animal Care and Use Committee of Massachusetts General Hospital and Massachusetts Institute on Technology.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics

Immunohistochemistry studies were conducted on breast cancer tissues from 11 patients diagnosed with metastatic breast cancer

BRISQ Summary/Checklist:
Biospecimen type: paraffin section. Available from pathology library (Mass General Brigham)
Type of long-term preservation Formalin fixation
Anatomical site: Breast and patient-matched brain metastasis (women).
Vital State of patients: Postmortem
Clinical diagnosis of patients: Breast cancer

Recruitment

No recruitement involded.

Ethics oversight

Tissue sections where obtained from Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH). This study was approved by the Institutional Review Board at BWH and MGH.

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	Cells isolated from tumor-derived organotypic slice cultures.
Instrument	LSRII
Software	FlowJo (version 10.4)
Cell population abundance	Only HER2+ tumor cells, representing 30-50% of viable cells quantified, were analyzed in live dead assay.
Gating strategy	Based on the pattern of FSC-A/SSC-A, cells were used for analysis of tumor cells. Singlets were gated according to the pattern of FSC-H vs FSC-A. Positive populations were determined by the specific antibodies, which were distinct form negative populations.

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