nature portfolio

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Reporting Summary

Nature Portfolio 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 Portfolio 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 custom code was developed or used in this study.
Data analysis	Data were analyzed using GraphPad Prism (v9) and FlowJo (v10). RNA-seq data were processed using Trim Galore for quality control, aligned to the mouse reference genome (GRCm39) using STAR, and quantified using featureCounts. Differential gene expression analysis was performed in R using DESeq2.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

ATAC-seq data have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE309615, and RNA-seq data are available under accession number GSE318085. Proteomics data have been deposited in the MassIVE repository under accession number MSV000099648 (doi: 10.25345/C56W96P1P).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Human samples were obtained from previously conducted clinical studies and institutional resources. Information on sex was recorded where available; however, sex- or gender-based analyses were not a primary focus of this study. Therefore, no stratified analysis by sex or gender was performed.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity information were not collected or were not available for the samples used in this study. Accordingly, analyses based on these variables were not performed.
Population characteristics	Human samples included peripheral blood mononuclear cells (PBMCs) and tumor specimens from cancer patients. Tumor-associated myeloid cells were analyzed using commercially purchased tissue microarrays (TMAs) representing triple-negative breast cancer (TNBC), prostate cancer, and oral cavity squamous cell carcinoma (OCSCC), as described in Fig. 3. PBMC samples from metastatic castration-resistant prostate cancer (mCRPC) patients and healthy donors were also included where indicated.
Recruitment	Tissue microarray (TMA) slides were obtained from commercial vendors. PBMC samples were obtained from previously conducted clinical studies and institutional biorepositories. No additional participant recruitment was performed for this study.
Ethics oversight	All human samples were obtained under protocols approved by the appropriate Institutional Review Board (IRB), or provided by commercial vendors in compliance with ethical regulations. All participants provided informed consent where applicable. Analyses were performed on de-identified samples, and investigators were blinded to clinical information during data collection and analysis. For clinical trial–derived PBMC samples, data were obtained from a previously registered study (ClinicalTrials.gov identifier: NCT04207255).

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

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 sizes were determined based on prior experience and standard practices in the field. No formal statistical methods were used to predetermine sample size. Group sizes were sufficient to ensure reproducibility across independent experiments.
Data exclusions	No data were excluded from the analyses unless predefined technical issues were identified. Any exclusions were applied consistently across all experimental groups.
Replication	All experiments were independently repeated at least five times with similar results. Representative data are shown where appropriate, and all attempts at replication were successful.
Randomization	Animals were randomly assigned to experimental groups where feasible. For in vitro experiments, samples were processed under identical conditions to minimize potential bias.
Blinding	Investigators were not blinded during data collection and analysis due to the nature of the experimental design. However, objective and standardized analysis methods were used, and for human sample analyses, investigators were blinded to clinical information.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	All antibodies used in this study are listed in the Key Resources Table (Supplementaty Table 1), including supplier, catalog number, and clone information and Antibody identifier.
Validation	All antibodies were validated by the manufacturers for the indicated applications and species. In addition, antibody performance was confirmed by appropriate controls and consistent staining patterns in our experimental system.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Murine cell lines including EL4 (ATCC TIB-39), B16-F10, 4T1, and MB49, as well as the human ovarian cancer cell line SK-OV3, were obtained from ATCC or established laboratory stocks.
Authentication	Cell lines were obtained from commercial sources (e.g., ATCC) or established laboratory stocks and were used at low passage numbers. Authentication was not performed after receipt; however, cell identity was routinely monitored based on morphology and growth characteristics.
Mycoplasma contamination	All cell lines were validated to be mycoplasma-free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines (as listed in the ICLAC database) were used in this study.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	C57BL/6, B6-Rag-/-, and Pmel mice were obtained from Jackson Laboratory (Bar Harbor, ME). SphK1 KO and SphK2 KO mice were a kind gift from Besim Ogretmen (MUSC). LyMCreACC-DKO mice were a kind gift from Norbert Leitinger (University of Virginia). The myeloid-specific ACC1 knockout mice were generated in-house by crossing Acacatm1Jdh/J (Acc1 flox) mice with LysM-Cre mice (Jackson Laboratory). Animals were maintained under specific pathogen-free conditions, and all experimental procedures were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) of the Medical University of South Carolina, Charleston (Protocol No. IACUC-2018-00628-2). For tumor experiments, an equal number of age- and gender-matched (both male and female) mice were randomly assigned for the experiments when they were between 8-10 weeks old to minimize the bias of sex.
Wild animals	N/A
Reporting on sex	An equal number of age- and gender-matched (both male and female) mice were randomly assigned for the experiments to minimize the bias of sex.
Field-collected samples	N/A
Ethics oversight	All animal experiments were conducted in accordance with institutional guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC) of the Medical University of South Carolina (Protocol No. IACUC-2018-00628-2).

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Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

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 were prepared from tumors, spleens, or in vitro cultures. Standard staining protocols were used.
Instrument	Data were acquired on BD LSRFortessa or FACSAria.
Software	Data was analyzed using FlowJo.
Cell population abundance	Post-sort purity of all isolated cell populations exceeded 90%, as confirmed by re-analysis of sorted fractions using flow cytometry with the same gating strategy used for initial cell identification.
Gating strategy	Gating included FSC/SSC selection, singlet discrimination, and marker-based identification. Gating strategies are provided in Supplementary Information.

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