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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 Authors & Referees 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	AlphaView v3.4 (Protein Simple); Living Image v4.5 (Perkin Elmer); FACSdiva v8 (BD Biosciences)
Data analysis	Analysis of previously published whole-exome sequencing data (TCGA-SKCM, Roh et al. and Riaz et al. studies) was performed using RStudio v1.1.3, R v3.5, samtools/bcftools 1.8, and the R packages 'TCGAbiolinks'/'survival'/'survminer as outlined in the methods section. Analysis of the MDACC GWAS study was performed using Plink v1.9, GenotypeHarmonizer v1.4.2, ShapeIt v2, and Impute2 as outlined in the methods section. Single cell RNA-sequencing was analyzed using Cell ranger v3.0.1 and Seurat v3.0.2. Gene set enrichment analysis was performed using the R package clusterProfiler v3.12. Flow cytometry data were analyzed with Flowjo v9.3. Immunofluorescent images for Endomucin and CD8+ stainings were analyzed using CellProfiler v3.1.8. All other graphs were generated using Graphpad Prism v8. Microsoft Excel v16 was used for data processing and t-test calculation.

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

All data analyzed from published studies are publicly available under the following accession numbers: TCGA-SKCM, dbGaP accession phs000178.v10.p8; MDACC GWAS study, phs000187.v1.p1; Roh et al. anti-PD1 treatment study, dbGaP BioProject ID PRJNA369259; Riaz et al. anti-PD1 treatment study, dbGaP BioProject ID PRJNA359359. Single-cell RNA-sequencing data has been deposited at the Gene Expression Omnibus (GEO) under accession number GSE146613. All other data are available from the corresponding author upon 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 samples for each group was empirically chosen based on knowledge on intragroup variation and expected effect size. Sample sizes for in-vitro experiments were chosen based on prior knowledge on intragroup variation (e.g., invasion and endothelial recruitment assays). No statistical methods were used to predetermine sample sizes.
Data exclusions	No data were excluded.
Replication	All in-vitro experiments were performed at least three times with similar results, and in-vivo experiments were performed at least twice with similar results.
Randomization	Samples were allocated randomly if possible. For experiments with genetically modified mice, allocation was performed according to genotype and mice were sex- and age-matched.
Blinding	Investigators were blinded for data collection for all in-vitro assays. No blinding was performed for in-vivo experiments due to cage labeling requirements.

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	CD45-BV785 (clone: 30-F11, supplier: BioLegend, cat#: 103149, lot#: B263597, dilution: 1:3,000), B220-BUV395 (RA3-6B2, BD Biosciences, 563793, 7177756, 1:400), CD11b-BV605 (M1/70, BioLegend, 101257, B256673, 1:6,000), CD11b-FITC (M1/70, BioLegend, 101206, B192968, 1:4,000), Ly6G-PerCP/Cy5.5 (1A8, Biolegend, 127616, B196548, 1:500), Ly6C-BV711 (HK1.4, BioLegend, 128037, B264621, 1:12,000), I-A/I-E-BV421 (M5/114.15.2, BioLegend, 107632, B234681, 1:9,000), F4/80-FITC (BM8, BioLegend, 123108, B222019, 1:500), CD24-PE (M1/69, BioLegend, 101808, B180221, 1:5,000), CD103-APC (2E7, BioLegend, 121414, B236942, 1:500), CD19-FITC (1D3/CD19, BioLegend, 152404, B233717, 1:1,500), TCRβ-PerCP/Cy5.5 (H57-597, BioLegend, 109228, B227995, 1:200), CD49b-APC (HMa2, BioLegend, 103516, B230857, 1:300), CD4-BV605 (GK1.5, BioLegend, 100451, B246547, 1:200), CD8α-AF700 (53-6.7, BioLegend, 100730, B205738, 1:1,000), Granzyme B-PE (QA16A02, BioLegend, 372208, B265797, 1:200), IFNγ-PE/Cy7 (XMG1.2, eBioscience, 25-7311-82, 4273965, 1:500), anti-Endomucin (V.7C7, Santa Cruz, sc-65495, F2618, 1:200), anti-CD8 (polyclonal, Synaptic Systems, 361003, 1:200).
Validation	Validation data of the antibodies listed above was performed by the manufacturers and is available at each manufacturer's website by searching under the provided antibody catalog numbers.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	B16F10, YUMM3.3, HUVEC, and Mewo cells were obtained from ATCC. YUMM1.7 and YUMMER1.7 cells were a gift from M. Bosenberg (Yale University).

Authentication	BRAF mutation present in the YUMM1.7 cell was validated by genotyping PCR. No other independent authentication was performed.
Mycoplasma contamination	Mycoplasma contamination in the cell lines was ruled out by regular PCR-based mycoplasma testing.
Commonly misidentified lines (See ICLAC register)	None.

Animals and other organisms

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

Laboratory animals	Human APOE-knock-in mice were obtained from Taconic Biosciences. C57Bl6j mice were obtained from Jackson laboratories. Mice for primary tumor growth and experimental metastasis assays were used at 7-10 weeks of age and were age- and sex-matched.
Wild animals	No wild animals were used in this study.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	All animals experiments were conducted in accordance with a protocol approved by the Institutional Animal Care and Use Committee at The Rockefeller 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	Tumor-infiltrating leukocytes were isolated using enzymatic digestion and Percoll gradient centrifugation as outlined in the methods section.
Instrument	BD LSR Fortessa
Software	BD DIVA software v8 was used for data collection and Flowjo software v9.3 was used for data analysis.
Cell population abundance	Cell population abundances in the post-sort fraction were not assessed.
Gating strategy	A gating strategy was followed as outlined in Supplementary Data Fig 2. In brief, an initial gate based on basal scatter characteristics served to exclude debris followed by singlet gates based on FSC-H and SSC-H. Compensation was calculated using single color controls using Ultracomp compensation beads (ThermoFisher) for antibodies and amine-reactive beads for Zombie (ThermoFisher).

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