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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	Attune NxT software V2.7.0; Cellquest Pro 5.2.1; IVIS LiveImage software 4.5.1.
Data analysis	Prism 7.0 (GraphPad), Cellprofiler v3.0, Cytobank v6.3.1, and ImageJ v1.8.0 software, BioGPS 2018, R 3.5.0, FlowJo 10.1.

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 generated or analyzed during this study are included in this published article (and its supplementary information files). Please contact the corresponding author for unique material requests. Some material used in the reported research may require requests to collaborators and agreements with both commercial and non-profit institutions, as specified in the paper. Requests are reviewed by Yale University to verify whether the request is subject to any intellectual property or confidentiality obligations. Any material that can be shared will be released via a Material Transfer Agreement.

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 methods were used to pre-determine sample size. Sample sizes were estimated based on preliminary experiments.
Data exclusions	No data were excluded throughout the studies.
Replication	Data were repeated for at least two times with consistent results. Data from representative experiment are shown and details are described in the paper.
Randomization	Random allocation was applied to this study. Tumor bearing mice were randomly assigned into treatment groups. Buffy coats were obtained from anonymous donors.
Blinding	For Tumor experiments, results were observed by someone blinded to the treatment groups. Pathological information were evaluated by pathologists blinded to the experimental conditions.

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

1. anti-S15 mAb (clone: m01, m03, 5G12 and IH3) in-house.
2. anti-CD3 mAb (clone: OKT3, cat#: 317101), BioLegend; anti-mouse CD3 (clone: 145-2C11, Cat#: 553057), BD; anti-mouse CD16/32(TruStain FcX™, Cat#: 101320),Biolegend; anti-PD-1 mAb (clone: RMPI-14, cat#: BE0146), anti-mouse IL-10 mAb (clone JES5-2A5,cat#: BE0049), anti-mouse CD8 mAb (clone YTS 169.4,cat#: BE0117), all from BioXCell (West Lebanon, NH). Anti-Mouse Pan-cytokeratin (CK, clone AE1/AE3,Cat#: ab27988), from Abcam. Polyclonal anti-mouse IgG HRP,Cat#: A9044-2ML, from Sigma.
3. APC-anti-CD8 (clone 53-6.7, cat#: 100711); PE anti-mouse CD4 (clone RM4-5, cat#: 100511); APC anti-CD8 (clone 53-6.7, cat#: 100711); BB700 anti-CD11b (clone M1/70,cat#: 101211); PE anti-F4/80 (clone BM8, cat#: 123109); a488 anti-CD11c (clone N418, cat#: 117313); BV421 anti-NK1.1 (clone PK136, cat#: 108731); FITC anti-Gr1 (clone RB6-8C5, cat#: 108405); BV421 anti-CD19(clone 6D5, cat#: 115505); BV510 anti-CD45(clone 30-F11, cat#: 103137); all from Biolegend.
anti-mouse IFN-g (clone XMG1.2, Cat#: 564336); anti-mouse TNF-a (clone MP6-XT22, Cat#: 506327); from BD.
4. Anti-Mouse CD45 (clone 30-F11), 141-Pr (Cat#: 3089005B); anti-Mouse CD11c (clone N418), 142-Nd, Cat#: 3142003B;anti-Mouse CD69 (clone H1.2F3), 143-Nd,Cat#: 3143004B; anti-Mouse CD45R (clone RA3-6B2), 144-Nd,Cat#: 3144011B;anti-Mouse CD4 (clone RM4-5), 145-Nd,Cat#: 3145002B;anti-Mouse F4/80 (clone BM8), 146-Nd,Cat#: 3146008B;anti-Mouse CD19 (clone 6D5), 149-Sm,Cat#: 3149002B;anti-Mouse Ly6-G (clone 1A8), 151-Eu,Cat#: 3151010B;anti-Mouse CD3e (clone 145-2C11), 152-Sm,Cat#: 3152004B;anti-Mouse CD8a (clone 53-6.7), 153-Eu,Cat#: 3153012B;anti-Mouse Foxp3 (clone FJK-16 s), 158-Gd,Cat#: 3158003A;anti-Mouse TBET (clone 4B10), 160-Gd,Cat#: 3160010B;anti-Mouse Ly6C (clone HK1.4), 162-Dy,Cat#: 3162014B; anti-Mouse PD-1 (clone 29F.1A12), 159-Tb, Cat#: 3159024B; anti-Mouse CD62L (clone MEL-14), 164-Nd,Cat#: 3164003B;anti-Mouse KI-67 (clone B56), 168-Er,Cat#: 3168007B;anti-Mouse NK1.1 (clone PK136), 170-Er,Cat#: 3170002B; anti-Mouse CD44 (clone IM7), 171-Yb,Cat#: 3171003B;anti-Mouse CD11b (clone M1/70), 172-Yb,Cat#: 3172012B;anti-Mouse Granzyme B (clone GB11), 173-Yb,Cat#: 3173006B;anti-Mouse LAG-3 (clone C9B7W), 174-Yb,Cat#: 3174019B;anti-Mouse CD127 (clone A7R34), 175-Lu,Cat#: 3175006B;anti-Mouse EOMES (clone Dan11mag), 176-Yb,Cat#:14-4875-80;anti-Mouse MHC class II (clone M5/114.15.2), 209-Bi,Cat#: 3209006B; all from Fluidigm.
Anti-Mouse CD25 (clone PC61), 150-Nd,Cat#: 102002;anti-Mouse TIM-3 (clone RMT3-23), 169-Tm, Cat#: 119702, all from

	Biolegend. Anti-Mouse KLRG-1 (clone 2F1), 154-Sm,Cat#: 16-5893-82; Thermo Fisher. Anti-Mouse B7-H1 (clone 10B5), 156-Gd; Anti-Mouse 4-1BB (clone 2A), 166-Er; all in house.
Validation	All the antibodies are validated for use in flow cytometry or CyTOF. Data are available on the manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	LOX IMVI, MC38 cell lines, NCI (Rockville, MD); U87, Jurkat E6-1, B16 and HEK 293T cell line, ATCC (Manassas, VA); GL261 cell line (Perkin Elmer); Jurkat NFAT-Luc cell line (Signosis).
Authentication	COA was provided with the cell lines by ATCC, NCI, Perkin Elmer or Signosis. Properties pertinent to the experiments (GFP/ Luciferase reporter expression or Siglec-15 expression) were confirmed by flow cytometry or IVIS imaging system.
Mycoplasma contamination	All cell lines were routinely tested for mycoplasma and were found to be negative.
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	Described in paper: female 6-8 week old, Charles River (Wilmington, MA): C57BL/6, BALB/c; Taconic Biosciences (Hudson, NY): OT-I/Rag-1 KO; Jackson Laboratory (Bar Harbor, ME): NZB/NZW F1; MMRRC, CA: Siglec-15 conditional knockout, C57BL/6 background;Jackson Laboratory (Bar Harbor, ME): CMV-Cre, LysM-Cre; Siglec-15 KO, whole-body S15 knockout, LysM-Cre S15KO myeloid lineage specific S15 KO mice (LysM-Cre KO). Sex matched S15 KO mice and WT littermates (~18 months of age) were used for phenotyping experiments.
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 mouse protocols were in accordance with NIH guidelines and were approved by the Institutional Animal Care and Use Committee of Yale University School of Medicine.

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	Described in paper.
Instrument	Attune NxT (ThermoFisher), BD Facs Calibur (BD Biosciences)
Software	Attune NxT software v2.7.0, Cellquest Pro 5.2.1, FlowJo 10.1
Cell population abundance	The purity was verified by flow cytometry.
Gating strategy	Described in paper.

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