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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Bio-Rad CFX Maestro Software version 1.1, FlowJo V10, R version 3.4.0, Bioconductor package edgeR
Data analysis	Graphpad Prism V6.02, FlowJo V10, inForm, PMOD v3.8, STAR v. 2.5.2b, TCGAbiolinks v.2.6.12, DESeq2 bioconductor R package v.1.18.1

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 upon request. 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

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are available in the NCBI BioSample repository under accession # SAMN09873568, SAMN09873569, https://www.ncbi.nlm.nih.gov/biosample/9873568, https://www.ncbi.nlm.nih.gov/biosample/9873569.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-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 using standard power calculations using p=0.05 and power = 70% and estimating effect size from previous studies. Given the difficult to generate mouse models employed (i.e. DIO, NIA caloric restricted, DIO Rag2 -/-, etc.), in certain experiments the sample size was dictated by the availability of a limited resource. For human studies sample size was based on the number of patients or volunteers enrolled to previously designed studies.
Data exclusions	Outliers were identified using R package "extreamvalues", and when present, were winsorized from the analysis, so that the outliers were set equal to the nearest non-outlier value using pre-established criteria. For human blood assays analysis of statistical outliers was undertaken once the spread of the data was determined. Statistical outliers were identified and excluded using Grubbs test using pre-established criteria.
Replication	All experiments were succesafully replicated two to three times except where otherwise noted in the manuscript. Two experiments (adoptive transfer) were not replicated due to the limited quantities of difficult to generate mouse models. A single murine B16 tumor experiment which was performed with a different clone of anti-PD-L1 antibody was excluded. The general results of this experiment were similar to previously performed experiments (performed in duplicate) although this anti-body did appear to have some T cell depleting effects.
Randomization	In all experiments groups receiving therapy were randomly chosen. In tumor experiments groups were not created randomly but rather stratified based on size of implanted tumor to ensure that tumor sizes were roughly equivalent between groups prior to initiating any therapy.
Blinding	Blinding was not possible during data collection as obese mice can be easily distinguished from non-obese mice. Data analysis for mouse studies was independently assessed in a blinded manner by a second reviewer.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants

Methods

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

Antibodies

Antibodies used	Human: anti-PD-1 (clone EH33, CST), anti-CD3 (polyclonal, DAKO), BV421-anti-CD3 (HIT3a, BD), BV605-anti-CD8a (RPA-T8, BioLegend), BV711-anti-CD4 (OKT4, BioLegend); PE-anti-PD-1 (EH12.2H7, BioLegend); APC-anti-Ki67 (20Raj1, eBioscience). NHP:CD3 (SP34-2, PB, BD), CD4 (L200, BV605, BD), CD8 (RPA-T8, AF700, BD), CD95 (DX2, APC, BD), CD28 (CD28.2, APC-H7, BD), PD-1 (EH12.2H7, PE, BioLegend), Ki67 (B56, AF488, BD). Mouse:anti-CD3 (clone SP7, Abcam) and anti-PD1 (clone EPR20665, Abcam), Fc block (anti-CD16/32 clone 93, BioLegend),): PB-anti-CD45 (30-F11), PB-anti-CD44 (IM7), APC-Cy7-anti-CD45 (30-F11), BV711-anti-CD4 (RM4-5), BV785-anti-CD3 (17A2), BV605-anti-CD8a (53-6.7), PE-Cy7-anti-TNFα (MP6-XT22), FITC-anti-CD11c (N418), APC-Cy7-anti-I-A/I-E (M5/114.15.2), AF700-anti-Ki67 (16A8); From eBioscience (San Diego, CA): PE-anti-PD-L1 (MIH5), PE-Cy7-anti-PD-1 (RMP1-30), PE-Cy7-anti-CD62L (MEL-14).
Validation	Please see table at the end of this form for antibody catalog numbers, dilutions used, and references pertaining to antibody validation.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	4T-1, Lewis Lung Carcinoma (3LL), B16F0, and B16F10 were obtained from the ATCC
Authentication	Mouse cell lines were recently obtained from ATCC recently and not separately authenticated
Mycoplasma contamination	All cell lines tested negative for mycoplasma contamination
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	Male and female C57BL/6NTac mice as well as male B6.129S6-Rag2tm1Fwa N12 (Rag2-/-) were purchased at 4 weeks age, generated into control or DIO mice and used between 6-12 months age as specified in the manuscript. B6.Cg-Lepob/J (ob/ob) mice and female B6.BKS(D)-Leprdb/J (B6 db/db) were used when they were 5-6 months old. 4-8 months old BKS.Cg-Dock7m +/+ Leprdb/J (BSK db/db) were used. 19 months old ad libitum (AL) and caloric restricted (CR) mice were obtained from the National Institute on Aging. For non-human primate studies blood was drawn from male Rhesus macaques (Macaca mulatta) from 6-10 years of age.
Wild animals	N/A
Field-collected samples	N/A

Human research participants

Policy information about studies involving human research participants

Population characteristics	For human healthy donor blood draws, blood was collected from 21 females mean age of 39 with age range of 27-60 and mean BMI of 30.4 and BMI range 18.8-50.6. In the human clinical study we analyzed data from 250 patients treated with PD-1/PD-L1 checkpoint inhibitors. For these patients mean BMI was 27.4, BMI range was 15-56.6, mean age was 61.7 and age range was 23-91, 45.6% were males. Fifty five patients had NSCLC, 45 had melanoma, 20 had ovarian, and 130 had other cancers. Seventy patients had ECOG performance status of 0, 134 had a performance status of 1, and 46 had a performance status of 2 or greater. Seventy patients had 1 prior line of therapy, 91 patients had 2 prior lines of therapy, and 115 patients had 3 or more prior lines of therapy.
Recruitment	For human healthy donor blood draws volunteers were recruited at the UC Davis Cancer Center. For the clinical study no specific recruitment strategy was employed as this was a retrospective analysis of patients previously treated with checkpoint inhibitors.

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	Single cell suspensions were prepared from livers, salivary glands, tumors, spleens and draining lymph nodes using manual disassociation and DNAase / collagenase
Instrument	LSR Fortessa flow cytometer (BD)
Software	FlowJo V10
Cell population abundance	Post sort cell populations were generally >95% as determined by flow cytometry
Gating strategy	Gating was performed using fluorescence minus one groups to set the negative gate. Gating strategies are demonstrated in representative flow plots throughout the manuscript.

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