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Last updated by author(s): August 8, 2024

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	ATAC-seq library preparation, DNA sequencing, and data collection were conducted at Azenta Life Sciences as noted in the methods section.
Data analysis	Codes used for this manuscript have been made available in the Github repository under the following link: https://github.com/hbc/HBC04813_Schatton_mouse_ATACseq/tree/main. ATAC-seq data quality was analyzed using ataqv. CPM-normalized bigwig files (bin size=20) were visualized using IGV. Qualitative assessment of the data indicated that sample untreated 1 had fewer peaks called (15,939) compared to all other samples (range 91,542-103,254), higher proportions of mono- and di-nucleosomal fragments and lower TSS enrichment. However, assessment of the peak overlap between the replicates untreated 1 and untreated 2 with ChIPpeakAnno v3.32.0 revealed that 69% of peaks called in untreated 1 overlapped with peaks called in untreated 2. Replicate data sets were thus merged using the bam files with Samtools v.1.14 to create pseudoreplicates using the (https://gist.github.com/brianhill11/7aeeeb6d94edfb868e5595aac04a0dd6) custom script. Peaks with unique reads were called using MACS2. Diffbind v3.4.11 was implemented in R 4.1.2 to generate a normalized count matrix for all samples. These count matrices were used in principal component analyses for all samples using the degPCA function from the DEGReport R package v.1.34.0. Differential accessibility was also assessed with Diffbind using DESeq2. Peaks were considered differentially enriched at FDR < 0.05. The initial count matrix was subset to only include differentially accessible regions and then a random subsample (3000 sites) was used to generate a heatmap with the pheatmap R package 1.0.12. Variability in read density of the Pdcd1 and Cd274 genes was examined and counts generated for 100 bp bins using the multiBamSummary function from deepTools. Counts were manually normalized by library size and smoothed conditional means plotted using the geom_smooth function from the R package ggplot2. Identical genomic regions were plotted using the gviz package implemented in R. Predicted STAT1, STAT2, and IRF9 binding sites were identified from the JASPAR database.

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

Murine ATAC-seq raw data have been deposited into the Gene Expression Omnibus (GEO) database under the following accession numbers: GSM8015946, GSM8015947, GSM8015948, GSM8015949, GSM8015950, GSM8015951 [https://www.ncbi.nlm.nih.gov/geo/ query/acc.cgi?acc=GSE253179]. The scRNA-seq publicly available data used in this study are also available in the GEO database under accession codes GSE72056 [https://www.ncbi.nlm.nih.gov/geo/ query/acc.cgi?acc=GSE72056] and GSE185386 [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc= GSE185386]. Source data are provided as a Source Data file, which is publically available within the Harvard Dataverse under the following link: https://doi.org/10.7910/DVN/JRJUMR.

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	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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 chosen based on experience and contingency table analyses (http://vassarstats.net/tab2x2.html). Numbers reflect the sample sizes needed to detect significant differences between experimental and control groups. E.g. our analyses indicated that a minimum of n=6 mice per group would be anticipated to yield sufficient statistical power to determine significant differences.
Data exclusions	No data was excluded from any of the reported analyses.
Replication	All results were confirmed in at least n=3 biologically independent experiments.
Randomization	For all in vivo tumorigenicity studies, gender and age-matched mice or equal genotype were randomly assigned to cages prior to tumor cell inoculation.
Blinding	n/a

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[ ]	[x] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

The following antibodies (abs) were used for flow cytometric analyses of human cells: Alexa Fluor 647-conjugated (BD Biosciences) or PerCP-eFluor 710-conjugated anti-human PD-1 (clone MIH4, 20 µg/mL, Thermo Fisher Scientific, Waltham, MA) and Alexa Fluor 647-conjugated or PerCP-eFluor 710-conjugated mouse IgG1 isotype controls (clone MOPC-31C, 20 µg/mL, BD Biosciences; clone P3.6.2.8.1, 20 µg/mL, Thermo Fisher Scientific), unconjugated anti-human PD-1 clinical ab, nivolumab (100 µg/mL, Bristol Myers Squibb, Cambridge, MA) was obtained from the BWH Pharmacy, and Ultra-LEAF unconjugated human IgG4 isotype control (clone QA16A15, 100 µg/mL, BioLegend), FITC-conjugated or PE-conjugated anti-human IgG4 (clone HP6023, 1:50, Abcam, Waltham, MA), PE-conjugated anti-human PD-L1 (clone 29E.2A3, 15 µg/mL, BioLegend) and PE-conjugated mouse IgG2b isotype control (clone MPC-11, 15 µg/mL, BioLegend), APC-conjugated anti-human PD-L2 (clone 24F.10C12, 15 µg/mL, BioLegend) and APC-conjugated mouse IgG2a isotype control (clone MOPC-173, 15 µg/mL, BioLegend), PE-conjugated anti-human IFNAR1 (clone 85228, 20 µg/mL, Thermo Fisher Scientific) and PE-conjugated mouse IgG1 isotype control (clone P3.6.2.8.1, 20 µg/mL, Thermo Fisher Scientific) or PE-conjugated mouse IgG1 isotype control (clone MOPC-21, 20 µg/mL, BioLegend), Alexa Fluor 750-conjugated anti-human IFNAR1 (clone 85228, 20 µg/mL, R&D Systems, Minneapolis, MN) and Alexa Fluor 750-conjugated mouse IgG1 isotype control (clone 11711, 20 µg/mL, R&D Systems), APC-conjugated or APC-Vio770-conjugated anti-human IFNAR2 (clone REA124, 20 µg/mL, Miltenyi Biotec, Gaithersburg, MD) and APC-conjugated or APC-Vio770-conjugated human IgG1 isotype control (clone REA293, 20 µg/mL, Miltenyi Biotec), FITC-conjugated anti-human IFN-β (clone A1(IFNb)), 5 µg/mL, and FITC-conjugated mouse IgG1 (clone MOPC-21, 5 µg/mL, Thermo Fisher Scientific), PE-conjugated anti-human IFN-[2b] (clone 7N4-1, 1.5 µg/mL) and PE-conjugated mouse IgG1 isotype control (clone MOPC-21, 1.5 µg/mL, BD Biosciences), FITC-conjugated anti-mouse Interferon alpha (clone RMMA-1, 50 µg/mL, PBL Assay Science, Piscataway, NJ) and FITC-conjugated rat IgG1 (clone eBRG1, 50 µg/mL, Thermo Fisher Scientific), anti-mouse Interferon-beta 1 (clone D2J1D, 75 ng/mL), rabbit IgG isotype control (clone DA1E, 75 ng/mL Cell Signaling Technology, Danvers, MA), and PE-conjugated donkey anti-rabbit IgG (clone Poly4064, 1.25 µg/mL BioLegend). The following abs were used to assess expression of JAK-STAT pathway proteins by intracellular flow cytometry: PE-conjugated anti-phospho (p)-STAT1 (Tyr701, clone 58D6, 1 µg/mL), PE-conjugated or Alexa Fluor 488-conjugated anti-p-STAT2 (Tyr690, clone D3P2P, 5 µg/mL), and PE-conjugated or Alexa-Fluor 488-conjugated rabbit IgG isotype control (clone DA1E, 1 and 5 µg/mL, respectively) (all from Cell Signaling Technology), APC-conjugated anti-p-JAK1 (Tyr1034 and Tyr1035, clone Jak1Y10221023-F11, 5 µg/mL, Abcam) and APC-conjugated rabbit IgG (clone EPR25A, 5 µg/mL, Abcam).

The following abs and/or reagents were used for flow cytometric analyses of murine cells: PE/Cyanine 7-conjugated or BV785-conjugated anti-mouse CD3 (clone 17A2, 10 µg/mL, BioLegend) and PE/Cyanine 7-conjugated or BV785-conjugated rat IgG2b isotype control (clone RTK4530, 10 µg/mL, BioLegend), Pacific Blue-conjugated or BV650-conjugated anti-mouse CD8a (clone 53-6.7, 10 µg/mL, BioLegend) and Pacific Blue-conjugated or BV650-conjugated rat IgG2a isotype control (clone RTK2758, 10 µg/mL, BioLegend), BV711-conjugated anti-mouse NK-1.1 (clone PK136, 10 µg/mL, BioLegend) and BV711-conjugated mouse IgG2a isotype control (clone MOPC-173, 10 µg/mL, BioLegend), BV570-conjugated anti-mouse CD11c (clone N418, 10 µg/mL, BioLegend) and BV570-conjugated armenian hamster IgG isotype control (clone HTK888, 10 µg/mL, BioLegend), BV605-conjugated anti-mouse CD45 (clone 30-F11, 10 µg/mL, BioLegend) and BV605-conjugated rat IgG2b isotype control (clone RTK4530, 10 µg/mL, BioLegend), Pacific Blue-conjugated anti-mouse CD31 (clone 390, 10 µg/mL, BioLegend) and Pacific Blue-conjugated rat IgG2a isotype control (clone RTK2758, 10 µg/mL, BioLegend), PE/Dazzle 594-conjugated anti-mouse CD140a (clone APA5, 10 µg/mL, BioLegend) and PE/Dazzle 594-conjugated rat IgG2a isotype control (clone RTK2758, 10 µg/mL, BioLegend), PE/Dazzle 594-conjugated or APC-eFluor 780-conjugated anti-mouse CD4 (clone GK1.5, 10 µg/mL, Thermo Fisher Scientific) and PE/Dazzle 594-conjugated or APC-eFluor 780-conjugated rat IgG2b isotype control (clone eB149/10H5, 10 µg/mL, Thermo Fisher Scientific), APC-eFluor 780-conjugated MHC Class I (H-2Kb, clone AF6-88.5.5.3, 5 µg/mL, Thermo Fisher Scientific), APC-eFluor 780-conjugated MHC Class I (H-2Kd, clone SF1-1.1.1, 5 µg/mL, Thermo Fisher Scientific) and APC-eFluor 780-conjugated mouse IgG2a isotype control (clone eBM2a, 5 µg/mL, Thermo Fisher Scientific), Alexa Fluor 700-conjugated anti-mouse CD19 (clone 1D3/CD19, 25 µg/mL, BioLegend) and Alexa Fluor 700-conjugated rat IgG2a isotype control (clone RTK2758, 25 µg/mL, BioLegend), RB705-conjugated rat anti-mouse CD11b (clone M1/70, 1.25 µg/mL, BD Biosciences) and RB705-conjugated rat IgG2b isotype control (clone R55-38, 1.25 µg/mL, BD Biosciences), PE/Cyanine 7-conjugated anti-mouse F4/80 (clone BM8, 10 µg/mL, BioLegend) and PE/Cyanine 7-conjugated rat IgG2a (clone RTK2758, 10 µg/mL, BioLegend), FITC-conjugated, APC-conjugated, PE-conjugated, PerCP/Cyanine 5.5-conjugated or Brilliant Violet 421-conjugated anti-mouse PD-1 (clone 29F.1A12, 20 µg/mL, BioLegend) and FITC-conjugated, APC-conjugated, PE-conjugated, PerCP/Cyanine 5.5-conjugated or Brilliant Violet 421-conjugated rat IgG2a isotype control (clone RTK2758, 20 µg/mL, BioLegend), PE-conjugated anti-mouse PD-L1 (clone 10F.9G2, 20 µg/mL, BioLegend) and PE-conjugated rat IgG2b isotype control (clone RTK4530, 20 µg/mL, BioLegend), PE-conjugated anti-mouse IFNAR1 (clone MAR1-5A3, 20 µg/mL, BioLegend) and PE-conjugated mouse IgG1 isotype control (clone MOPC-21, 20 µg/mL, BioLegend), PE-conjugated or APC-conjugated anti-mouse IFNAR2 (clone Q9D1R7, 20 µg/mL, R&D Systems) and PE-conjugated or APC-conjugated goat IgG isotype control (20 µg/mL, R&D Systems). Flow cytometric analyses additionally included the following reagents: Human TruStain FcX (Fc Receptor Blocking Solution, 1:20), TruStain FcX PLUS Antibody (anti-mouse CD16/32, clone S17011E, 2.5 µg/mL), Zombie NIR Fixable Viability Kit, Zombie Aqua Fixable Viability Kit, and Zombie Green Fixable Viability Kit (all from BioLegend, 1:1000).

The following abs were used for Western blotting: anti-phospho STAT1 (Tyr701, clone 58D6, 1:1000), anti-STAT1 (clone D1K9Y, 1:1000), anti-STAT1 (clone D4Y6Z, 1:1000), anti-phospho STAT2 (Tyr690, clone D3P2P, 1:1000), anti-STAT2 (clone D9J7L, 1:1000), anti-phospho JAK1 (Tyr1034/Tyr1035, clone D7N4Z, 1:1000), anti-JAK1 (clone 6G4, 1:1000), anti-phospho Tyk2 (Tyr1054/Tyr1055, clone D7T8A, 1:1000), anti-Tyk2 (clone D4I5T, 1:1000) (all from Cell Signaling Technology) anti--actin (clone C4, 1:10000, BD

Biosciences), and horseradish peroxidase (HRP)-conjugated anti-rabbit or anti-mouse (Cell Signaling Technology). The following abs from Cell Signaling Technology were used for chromatin immunoprecipitation and quantitative polymerase chain reaction (ChIP-qPCR): anti-p-STAT1 (Tyr701, clone 58D6, 0.59 µg), STAT2 (clone D9J7L, 0.77 µg) and anti-IRF9 (clone D9I5H, 1.33 µg).
The following abs were used for in vitro and/or in vivo inhibition experiments (concentrations shown under 'Recombinant cytokine treatment' and/or 'In vivo tumorigenicity studies', respectively): InVivoMAb anti-human PD-1 (clone J116, Bio X Cell, Lebanon, NH) and InVivoMAb mouse IgG1 isotype control (clone MOPC-21, Bio X Cell), anti-human IFNAR1 clinical ab, anifrolumab (MedChemExpress, Monmouth Junction, NJ), and Ultra-LEAF Purified human IgG1 isotype control (clone QA16A12, BioLegend), Ultra-LEAF Purified anti-mouse PD-1 (clone 29F.1A12, BioLegend) and Ultra-LEAF Purified rat IgG2a isotype control (clone RTK2758, BioLegend), Ultra-LEAF Purified anti-mouse IFNAR1 (clone MAR1-5A3, BioLegend) and Ultra-LEAF Purified mouse IgG1 isotype control (clone MOPC-21, BioLegend).

Validation

All antibodies used for our study are commercially available, have been validated as per the manufacturer's product sheet, numerous independent references, and also by our laboratories via the use of appropriate negative and positive controls.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Authenticated, mycoplasma-free human A2058 (CRL-3601), A375 (CRL-1619), G361 (CRL-1424), MeWo (HTB-65), MDA-MB-435S (HTB-129), and SK-MEL-2 (HTB-68), and murine B16-F10 (CRL-6475), YUMM1.7 (CRL-3362), YUMMER1.7D4 (SCC243), YUMM1.G1 (CRL-3363), YUMM4.1 (CRL-3366), and YUMM5.2 (CRL-3367) melanoma cell lines were obtained from the American Type Culture Collection (ATCC, Gaithersburg, MD) or MilliporeSigma (St. Louis, MO).
Authentication	STR profiling
Mycoplasma contamination	We routinely test our cell lines for mycoplasm contamination using the Roche mycoplasma detection kit.
Commonly misidentified lines (See ICLAC register)	n/a

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 and nonobese diabetic/severe combined immunodeficiency (NOD/SCID) interleukin (IL)-2Rg(-/-) KO (NSG) mice were purchased from the Jackson Laboratory (Bar Harbor, ME). Age- and sex-matched mice of at least 6 weeks of age were used for all experiments.
Wild animals	n/a
Reporting on sex	Both male and female mice were used in our study.
Field-collected samples	n/a
Ethics oversight	All mice were used in accordance with the National Institutes of Animal Healthcare Guidelines under the BWH IACUC-approved experimental protocol 2016N000112. The study is reported in accordance with ARRIVE guidelines.

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

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	Melanoma cell lines were harvested with 1 mM EDTA (Thermo Fisher), passed through a 70 µm nylon mesh (Thermo Fisher), resuspended in PBS containing 2% FBS (Invitrogen) and subsequently stained with fluorescent antibodies for FACS analysis.
Instrument	Aurora Spectral Viewer (Cytek, Fremont, CA)
Software	FlowJo v10.10 (TreeStar, Ashland, OR)
Cell population abundance	We collected data on at least 10,000 cells per experimental condition.
Gating strategy	All expression gates were set based on isotype control staining (< or = 0.5-1%). FSC-SSC gates were set to exclude cell debris (small FSC/SSC) and cell doublets, and include a defined population showing FSC/SSC parameters indicative of tumor cells or other cell types based on experience. Nonviable cells were excluded using the Zombie NIR Fixable Viability Kit or Zombie Green Fixable Viability Kit, as per the manufacturer's recommendations. We included complete gating strategies in the supplement.

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