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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 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	The complete data collection is described in depth in the methods section. Equipment used for data collection comprised FACS Aria III (BD) and Attune Nxt (Thermo-Fisher) for flow cytometry, Illumina-HiSeq-1500 for CNV (Marburg), Illumina-NovaSeq-6000 for WES (Macrogen, Seoul), Illumina-HiSeq-4000 for RNAseq (Beijing Genomic Institute), FUJIFILM Visual Sonics Vevo 2100 (Marburg) for ultrasound imaging, StepOnePlus cycler (AppliedBiosystems) for qRT-PCR
Data analysis	The detailed methods of data analysis are provided in the methods section of the article. Custom code used for the generation of plots in the article has been deposited here (https://github.com/Das-Gupta-D/Lohoff-Lab) as R project files combined with normalized and filtered read tables.

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 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 RNA sequencing datasets generated during the current study have been deposited in the Gene Expression Omnibus (GEO) archive and are available under the accession number GSE157958. The WES datasets are currently in the process of submission for deposition in the Sequence Read Archive (SRA). The accession number will be made available shortly.

Other data generated in this study is available from the corresponding author upon individual 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	For ex vivo experiments no preanalytical determinations of sample size were conducted. For in vivo experiments we used an effect size calculation using Cohen's D, demanding a power of greater than 90 %.
Data exclusions	no data was excluded from analysis.
Replication	A minimum of three replicates from biologically distinct samples was conducted for each experiment. The number of biological replicates is stated in each figure and figure legend.
Randomization	Refer to the corresponding method section for details regarding the in vivo experiment. For ex vivo analyses and experiments, no randomization was employed.
Blinding	Investigators were not blinded to treatment groups in the in vivo experiment. As the substance formulations and vehicle controls showed marked differences in color, a blinding was not feasible during treatment.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	The antibodies used in this study are detailed in the respective part of the methods section. Information about clones, companies and dilutions used are provided for all antibodies. Flow cytometry: B220 (RA3-6B2, Biolegend), IgM (II/41, BD), CD2 (RM2-5, Biolegend), CXCR4 (L276F12, Biolegend), CD127 (=IL-7Rα) (A7R34, BD Bioscience), CD179b (=λ5) (LM34, BD Bioscience) Histological stainings: CD45R/B220 (clone RA3-6B2, BD), KI67 (clone TEC-3, Dako) Western Blotting: FAK (AHO0502, Invitrogen), goat anti-rabbit IgG HRP (sc-2004, Santa Cruz), beta-Actin (AC-15, Sigma-Aldrich), goat anti-mouse HRP (sc-2055, Santa Cruz)
Validation	The validation of all primary antibodies was performed by the manufacturers. Dilution and blocking agents for all antibodies were based on manufacturers' recomendations and tested for our individual experimental setup.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293t/17 cells were aquired from ATCC. T8.1, T8.2 and T11 cells were established from primary tumours first described in this study, as detailed in the methods section of the article. ST2 cells were provided by colleagues from DRFZ in Berlin. Eμ-Myc transgene driven murine 35911 preB cell line was provided by colleagues in Marburg, who had previously reported their generation: A detailed description is supplied with the method section of the article.
Authentication	HEK293t/17 cells were authenticated by the supplier. Cells for the generation of viral supernatant were between 1 and 20 passages old.
Mycoplasma contamination	All cell cultures established from thawed cryo stocks tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Animals and other organisms

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

Laboratory animals	All mice used for ex vivo analyses and experiments were from C57BL/6J background. The Irf4 KO mice used in this study are B6.129P2-Irf4tm1Mak/J mice. All mice were age and sex matched. For in vivo experiments we used female C57BL/6J acceptor mice at 8 weeks of age. Details can be found in the corresponding method section of this article.
Wild animals	N/A
Field-collected samples	N/A
Ethics oversight	All mouse experiments were approved by the local committtee (Regierungspräsidium Gießen, case number: G49/2018)

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	The sample preparation differed between experiments and is detailed individually in the corresponding method sections of the article.
Instrument	FACS Aria III (BD, sorting and analysis), Attune Nxt (Thermo-Fisher, analysis)
Software	FlowJo V10.7.1
Cell population abundance	The purity of sorted populations was analyzed immediately after sorting on the FACS Aria III and always exceeded 95 % purity.
Gating strategy	We identified lymphocytes by FSC-A/SSC-A gaiting and subsequently excluded doublets by pulse height/area plotting (FSC-H/FSC-A). Further gating was dependent on the employed marker panel and is detailed in the figures, figure legends and method section.

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