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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	Microsoft Office v15.41; BD FACSDiva 8.0.1; Microsoft Office; Zen 2 image analysis software; Volocity (v6.2, Perkin Elmer)
Data analysis	All statistical analyses were determined with Prism 7.0 version. BD FACSDiva 8.0.1; Microsoft Office v15.41; Zen 2 image analysis software; Volocity (v6.2, Perkin Elmer); R-Studio; Cellranger pipeline of 10X Genomics (version 2.1.1); DESeq (v1.22.2, R 3.5.2); edgeR (v3.24.3, R 3.5.2); scater (v1.10.1, R 3.5.2); scran (v1.10.2, R 3.5.2); destiny (v2.12.0, R 3.5.2); M3Drop (v1.8.1, R 3.5.2); ToppGene (toppgene.cchmc.org); ToppCluster (toppcluster.cchmc.org); keras (2.2.4.1); lime (0.4.1). Corel DRAW Graphics Suite X7; Adobe Acrobat Pro DC, Adobe Photoshop CC2019

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

RNA–seq data that support the findings of this study have been deposited in the Gene Expression Omnibus (GEO) under accession code GSE130299. Previously published sequencing data that were re-analysed here are available under ArrayExpress E-MTAB-4547. All other data supporting the findings of this study are available from the corresponding author on reasonable 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	In order to choose sample size, we used GraphPad StatMate Software Version 2.0b, estimating a standard deviation between 2 and 8 (depending on the experiment).
Data exclusions	Some of the recipient mice in the transplant experiments were excluded from the final analysis because they failed to meet criteria for engraftment (i.e. contribution to at least 0.1% of total white blood cells in peripheral blood after 20weeks from transplant). Criteria for exclusions were pre-established.
Replication	Experiments were replicated using always the same machines, instruments and softwares for data collection and analysis. quality and robustness of instruments were regularly checked before each experiment. Technical support in sample preparations was also always the same throughout the experiments in the studies. All samples and mice were handled following the same protocols.
Randomization	Samples allocation was random and mice for experiments were randomly chosen.
Blinding	The investigator was not blinded to the mouse group allocation nor when assessing the outcome of experiments (Rag2-/-gammac-/-KitW/Wv mice and aged mice require particular care and follow up).

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	Information about all antibodies used in this study and their validation has been provided in Supplementary Table 6.
Validation	Information about all antibodies used in this study and their validation has been provided in Supplementary Table 6.

Animals and other organisms

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

Laboratory animals	All C57/Bl6 mice were females and derived from in-house colonies or from commercial suppliers. Nestin-GFP mice were on a C57/BL6 background and were derived by in-house colonies. Rag2-/-gc-/-KitW/Wv mice were derived from in-house colonies. Young C57Bl6 were 10-16 week old. Old C57BL6 mice were 80-110 week old. Young Rag2-/-gc-/-KitW/Wv recipient mice were 5-10 week old. Old Rag2-/-gc-/-KitW/Wv recipient mice were 56-64 week old.
Wild animals	The study didn't involve wild animals
Field-collected samples	The study didn't involve samples collected from the field.

Ethics oversight	All mouse experiments were performed in compliance with the German Law for Welfare 289 of Laboratory Animals and were approved by the Institutional Review Board of the University of Ulm as well as by the Regierungspraesidium Tuebingen (state government of Baden-Württemberg)

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	All bone marrow and peripheral blood samples were prepared freshly the same day of the experiment. In the case of peripheral blood samples, after blood collection samples were briefly stored on ice and stained within 1 hour from collection. Flow cytometry analyses were always performed within the following 3-4 hours. The samples were accurately stored on ice in the dark till flow cytometric analysis. As for bone marrow samples, bone marrow was flushed from long bones after the mouse sacrifice and cells were immediately processed for staining. Samples were always stored on ice throughout the procedure. As for histology, bones were also processed immediately after the mouse sacrificed. After fixation, bones were stored at -80°C till the staining. Microscopy analysis was performed immediately after the staining and all images were collected within 24-48 hours from the final staining.
Instrument	BD FACS Aria III and LSRII (BD Bioscience)
Software	BD FACSDiva 8.0.1
Cell population abundance	Cells were not post-sorted. Mostly, cell abundance was microscopically checked: if the sorted cell number was below 100 cells, cells were microscopically counted to verify exact number; if sorted cell number was above 100 cells, samples were microscopically checked for relative equal amount.
Gating strategy	Gating strategy are shown in Extended Data Figures 1 and 8.

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