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Last updated by author(s): Feb 7, 2019

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	FACSDiva 8.0.2
Data analysis	Microsoft Excel, GraphPad Prism 7

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

RNAseq data from this study have been deposited to GEO with Access number GSE123527. DNA gel raw image data were included in the Supplementary Figure 7. Statistical source data were included in the Supplementary Table 3.

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

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were not pre-determined based on statistical power calculations. The sizes were determined based on previous published studies, experimental experience and knowledge.
Data exclusions	No data were excluded.
Replication	All experiments were repeated with independent biological replicates in independent experiments. All findings are reproducible.
Randomization	All mutant and control animals were gender-matched litter mates.
Blinding	All samples were not blinded to the authors. Bind experiments were not necessary as all measurements were objective.

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

The following antibodies were used for flow cytometry
CD34 FITC 1:100 BD Pharmingen 560238 RAM34
CD45.2 FITC 1:400 BioLegend 109806 104
CD45R FITC 1:400 BioLegend 103206 RA3-6B2
CD2 FITC 1:200 Invitrogen 1934090 RM2-5
CD5 FITC 1:400 BioLegend 100606 5.3-7.3
TER119 FITC 1:200 BioLegend 116206 TER-119
CD8A FITC 1:400 BioLegend 100706 53-6.7
CD3 FITC 1:200 BioLegend 100204 17A2
CD41 FITC 1:200 BioLegend 133904 MWREG30
GR1 FITC 1:400 BioLegend 108406 RB6-8C5
CD45.2 PE 1:400 BioLegend 109808 104
CD45R PE 1:400 BioLegend 103207 RA3-6B2
CD2 PE 1:200 BioLegend 100108 RM2-5
CD5 PE 1:400 BioLegend 100607 5.3-7.3
TER119 PE 1:200 BioLegend 116208 TER-119
CD8A PE 1:400 BioLegend 100708 53-6.7
CD3 PE 1:200 BioLegend 100206 17A2
CD41 PE 1:200 BioLegend 133905 MWREG30
GR1 PE 1:400 BioLegend 108408 RB6-8C5
CD48 PE 1:200 BioLegend 103405 HM48-1
CD150 PE 1:200 BioLegend 115904 TC15-12F112.2
CD150 APC 1:200 BioLegend 115909 TC15-12F112.2
CD48 APC 1:200 BioLegend 103412 HM48-1
CD16/32 APC 1:400 BioLegend 101325 93
CD11B APC 1:400 BioLegend 101212 M1/70
CD150 PE-CY5 1:200 BioLegend 115912 TC15-12F112.2
CD45R PE-CY5 1:400 BioLegend 103210 RA3-6B2
CD135 PE-CY5 1:100 BioLegend 135312 A2F10
CD11B PE-CY7 1:400 BioLegend 101216 M1/70
GR1 PE-CY7 1:400 BioLegend 108416 RB6-8C5
CD45.1 PE-CY7 1:200 BioLegend 110729 A20

SCA-1 PE-CY7 1:200 BioLegend 122514 E13-161.7
SCA-1 A700 1:200 BioLegend 108142 D7
CD45.1 APC-CY7 1:200 BioLegend 110716 A20
TER119 APC-CY7 1:200 BioLegend 116223 TER-119
C-KIT APC-CY7 1:200 BioLegend 105826 2B8
C-KIT BIOTIN 1:200 BioLegend 105804 2B8
CD127 BIOTIN 1:200 BioLegend 135005 A7R34
STREP PE 610 1:400 Invitrogen 1926020
STREP PE-CY7 1:400 BioLegend 405206
STREP APC-CY7 1:400 BioLegend 405208
BRDU APC 1:100 BD Pharmingen 51-23619L

Validation

They are all from commercial sources (BD Pharmingen, Biolegend or Invitrogen) and are widely used in the field. They are all validated by the manufacture on flow cytometry experiments.

Animals and other organisms

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

Laboratory animals	Mx1-cre, Lysm-cre, Rosa26-creER, Myc-GFP, Rosa-loxpMyc and Mettl3 fl mice. All of the mice were on B6 background. Both adult males and females (~2month old) are used in experiments.
Wild animals	No wild animals were used in this study.
Field-collected samples	No filed-collected samples were used in this study.
Ethics oversight	All experiments were approved by Columbia University Institutional Animal Care and Use Committee under protocol AC-AAAP7405.

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	Bone marrow cells were isolated by flushing the long bones or by crushing the long bones, pelvis, and vertebrae with mortar and pestle in Ca2+ free and Mg2+ free HBSS with 2% heat-inactivated bovine serum. Splenic cells were obtained by crushing the spleens between two glass slides. The splenic and bone marrow cells were passed through a 25G needle several times and filtered through 70um nylon mesh.
Instrument	Samples were run on FACSAria II, BD LSR II, FACSCanto or FACScelesta flow cytometers.
Software	FACSDiva v8.0.2 (BD) was used for data collection. FlowJo v10(Tree Star) software was used for data analysis.
Cell population abundance	The HSC frequency is about 0.007% in wild type bone marrow. It goes up to about 0.1% (14 fold higher in mutants).
Gating strategy	The gating strategy is illustrated in the figures (Supplementary Fig 2 and Supplementary Fig 6).

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