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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	To collect FACS data BD FACSDiva, for comet assays SPOT Advanced, for senescence-associated -galactosidase activity assay AxioVison 3.1 software was used.
Data analysis	Prism 7, Flow Jo 9.9.4, MetaMorph Microscopy Automation and Image Analysis Software, cBioPortal, For whole genome sequencing analysis we used: bwa mem (version 0.7.15-r1140),GEM software suite,VariantAnnotation,HipSTR version v0.4,GRIDSS version 1.3.4, RepeatMasker, software package ggbio.

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

Data are made available online under the accession number ENA:PRJEB25666.

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

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 chosen to observe statistically significant differences between control mice (or cells) and the genetically modified mice (cells) using online tools available at www.sample-size.net
Data exclusions	Mice that developed radiation induced thymic lymphoma of host origin (verified by L5.1 vs Ly5.2 expression) were excluded from animal survival curves.These criteria were predetermined before the start of the experiments.
Replication	All attempts of replication were successful
Randomization	Randomization was used for lethally irradiated C57BL/6-Ly5.1+ mice to perform HSPCs injections
Blinding	The investigator was blinded to the genotype of the cells that were examined by microscopy. The animal technicians looking after the mice and making the call on their sickness (leukemia/lymphoma) were blinded to the nature of the experiment

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☒ Unique materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☐	☒ Research animals
☐	☒ Human research participants

Unique materials

Obtaining unique materials	All the unique materials are made available by the authors

Antibodies

Antibodies used	FACS antibodies: B220 (RA3-6B2), IgM (5.1), IgD (11-26C), CD4 (H129), CD8 (YTS.169), MAC-1 (M1/70), and GR-1 (RB6-8C5). To confirm that the lymphomas or leukaemias were of donor haematopoietic cell derived origin, staining for Ly5.2 (5.405.15.2) was performed, in addition to verifying that they were GFP+. Antibodies were produced in our laboratory and conjugated to R-phycoerythrin (R-PE) or allophycocyanin according to the manufacturer's (Prozyme) instructions. FITC conjugated Annexin-V (Life Technologies), DAPI (vector Laboratories) Western blot antibodies: ZMAT3 (Sigma-Aldrich, AV50793), p53 (Novocastra, Leica, CM5) and MLH1 (Calbiochem, PC56). Monoclonal antibodies were used to detect mouse CAV1 (BD Biosciences, 610406) and HSP70 (clone N6; a gift from Dr Robin Andersson, Olivia Newton John Cancer Centre, Heidelberg, VIC, Australia). For checking mTOR activity, we blotted with the following antibodies from Cell Signalling: LC3B (D11), p-ULK1S757 (D7O6U), ULK1 (D8H5), p-S6S240/244 (D68F8), S6 (5G10), p-4E-BP1S65 (#9451), 4E-BP1 (53H11), and SQSTM1 (#5114). The antibody against b-actin (loading control) was purchased from Sigma (AC-15).
Validation	FACS antibodies were validated by demonstrating that they stain the cell types that express the surface markers detected by

these antibodies. Antibodies for Western blotting were validated by showing that they recognise a protein of the expected molecular weight and that the intensity of the protein band is reduced when cells are transduced with an shRNA targeting corresponding gene or by using cells deficient for that gene.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	WT MEFs were prepared from E13.5 embryos. A single cell suspension of the body (excluding head and foetal liver) was prepared. E-Myc 560 cell line was prepared from single cell suspension of lymphoma cells from sick Eμ-Myc lymphoma mice
Authentication	The cell lines were authenticated by flow cytometry and genotyping
Mycoplasma contamination	All cell lines tested were negative for Mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Research animals

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

Animals/animal-derived materials	In this work Cas9, Eμ-Myc, Eμ-Myc;Puma-/- , Puma-/-;p21-/-, Zmat3-/- and p53−/− mice were used (male and females, 8-12 weeks old, 20-25g body weight). For haematopoietic reconstitution, fresh embryonic day 13.5 (E13.5) foetal liver cells (a rich source of HSPCs) were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	This work does not involve human research participants

Method-specific reporting

n/a	Involved in the study
☐	☐ ChIP-seq
☐	☒ Flow cytometry
☐	☐ Magnetic resonance imaging

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*
Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*

Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

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	FACS analysis was used for immunophenotyping of lymphomas and leukaemias was performed on single-cell suspensions that had been stained with surface-markerspecific antibodies (detail description in Methods section).
Instrument	LSR IIW or FACS Calibur flow cytometers (Becton Dickinson)
Software	To collect data Diva software was used. Data analysis was preformed using FlowJo 9.9.4
Cell population abundance	Virally transduced cells were sorted using Aria W (Becton Dickinson) by enriching for eGFP-positive cells
Gating strategy	For immunophenotyping of lymphomas and leukaemias (Supplementary Figure 2) the flow cytometry profiles were gated preliminary on FSC/SSC lymphocytes population, then on live (PI-), and then on donor derived (GFP+) cells. Cell proliferation was monitored by DAPI staining of pre-leukaemic bone marrow derived B lymphoid cells followed by flow cytometric analysis. GFP +B220+ cells were regarded as donor-derived and vector transduced B cells (Supplementary Figure 7c,15c). Flow cytometric analysis of the dilution of CTV in B cells from Zmat3 mutant, wt and p53-/- mice, was assessed gating first on live B cells (B220+ and PI-). Cell viability (Supplementary Figure 16) was determined by staining with propidium iodide (PI) and analysed by flow cytometry, PI-GFP+ cells were regarded as viable cells. Cell viability of thymocytes from Zmat3 mutant, wt and p53-/- mice was determined by staining with PI plus FITC conjugated Annexin-V and analysed by flow cytometr PI- Annexin-V- cells were regarded as viable thymocytes.

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

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference
(See Eklund et al. 2016)

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.