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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	Mass spectrometry acquisition was performed using the Agilent Mass Hunter Data Acquisition software ver. B.05.00 Build 5.0.5042.2 and analysis was performed using Mass Hunter Qualitative Analysis ver. B.05.00 Build 5.0.519.13. X-ray diffraction data for all crystals were collected at the Australian Synchrotron (Clayton, Victoria, Australia) using Blue-ice software.
Data analysis	All software used is commercially or publicly available and described in the Methods section. Data displayed in graphs were generally analyzed using Stata/IC 12.1 (StataCorp) or for dose-response curves using GraphPad Prism 7b (GraphPadSoftware Inc.). RNA-seq data, crystallography data and medicinal chemistry data were analyzed with commercially or publicly available software, also as described in the Method section: SPR. Scrubber software (version 2c) was utilized for data processing and analysis (www.biologic.com.au). Crystallization studies, as described in the methods section: the structures were determined by molecular replacement with PHASER using search models. Structures were refined through cycles of manual building using COOT and refinement using PHENIX Refine. Restraint libraries were developed through PHENIX eLBOW32 Structure validation was monitored with MolProbity. RNA-seq: Rsubread was used to map reads to the mouse genome. Differential expression analyses were undertaken using the edgeR and limma software packages. Molecular signatures were analyzed using ROAST. Differentially expressed genes were prioritized using TREAT. For more details see methods section.

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

The RNA sequencing data of MEFs treated with WM-8014, WM-2474 and DMSO, of MEFs from Kat6a–/– and wild type embryos and of lymphoma cell line EMRK1184 with vehicle and WM-1119 have been submitted to the GEO database under accession number GSE108244. The crystal structure data for the MYST domain in complex with WM-8014, acetyl-CoA and WM-1119 have been submitted under accession numbers PDB accession codes 6BA2, 6BA4 and 6CT2, respectively. Source data for all graphs are provided in Supplementary File "Baell Thomas source data of all graphs April 2018.xlsx".

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 ☐ Ecological, evolutionary & environmental 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	We used up to three technical replicates of three to twenty biological replicates per experimental group per experiment. Each biological replicate represents an individual animal or a primary cell isolate from an individual animal. In compliance with animal ethics regulations, the numbers were the minimum numbers that allowed us to obtain a statistically meaningful results. They were smaller where large differences between experimental groups and small variances within experimental groups were observed.
Data exclusions	No data were excluded.
Replication	Experiments were replicated at least twice, as indicated in the figure legends. Experiment using animals or cells used a minimum of 3 independent biological replicates and, in the case of cell based assays 3 technical replicates.
Randomization	Age and sex matched samples were randomly assigned to experimental and control groups.
Blinding	Experimental results were obtained by automated methods (cell counter; flow cytometer; IVIS bioluminescence imaging; NextSeq sequencing; RT-qPCR; SPR).

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	All unique materials are readily available from the authors.

Antibodies

Antibodies used

The primary antibodies used are:
• rabbit monoclonal anti-H3K9ac (Cell signaling Technology, Danvers Massachusetts: C5B11) Lot : 11. Dilution for western blot:1:5000 Dilution for ChIP: 5 ul per 40 ul chromatin. Dilution for FACS: 1/500
• rabbit monoclonal anti-H3K14ac (Cell signaling Technology, Danvers Massachusetts: D4B9, #7627) Lot: 4. Dilution for western blot 1:5000 Dilution, for FACS: 1/500.
• rabbit polyclonal anti- H4 (Millipore, Temecula California: 05-858; 1:30,000).
• anti-γH2A.X (serine 139; clone: JBW301) biotin-conjugated antibody (1:400, Merck, Kenilworth, NJ, USA, cat: 16-193)
• anti-BrdU Flow Kit (BD Biosciences, 552598, diluted according to manufacturer's instructions)
• CD19-PeCy7 (clone 1D3, BD Biosciences # 561739, used at 1:200)
• B220-A700 (clone 16A, conjugated at WEHI, used at 1:200)
• IgM-A647 (clone II/41, conjugated at WEHI, used at 1:200)
• IgD-PE (clone 11-26c, conjugated at WEHI, used at 1:200)
• isotype control IgG antibody (clone DA1E, Rabbit mAb IgG XP® Isotype Control,#3900, Cell Signaling, lot49, Lot 29, Dilution for FACS: 1:500)

Validation

High-quality commercial antibodies tested by the source companies were used. Wherever possible monoclonal antibodies were used to ensure reproducibility.
• rabbit monoclonal anti-H3K9ac (Cell signaling Technology, Danvers Massachusetts: C5B11). Specificity determined by western blot.
• rabbit monoclonal anti-H3K14ac (Cell signaling Technology, Danvers Massachusetts: D4B9, #7627) specificity determined by western blot.
• rabbit polyclonal anti- H4 (Millipore, Temecula California: 05-858). Manufactures report: "Routinely evaluated by western blot: This lot detected unmodified recombinant histone H4 protein (Catalog # 14-412) and histone H4 in acid extracts from both untreated HeLa cells and cells treated with sodium butyrate (hyper-acetylated) or colcemid (hyper-phosphorylated)".
• anti-γH2A.X (serine 139; clone: JBW301) biotin-conjugated antibody (Merck, Kenilworth, NJ, USA, cat: 16-193). Manufactures report: "Anti-phospho-Histone H2A.X (Ser139), clone JBW301 is a Mouse Monoclonal Antibody validated in ChIP, ICC, IF, WB. This purified mAb is highly specific for phospho-Histone H2A.X (Ser139) also known as H2AXS139p".

Flow cytometry to identify blood cell populations via cell surface markers used validated monoclonal antibodies either from commercial suppliers or produced from hybridomas in house.
• CD19-PeCy7 (clone 1D3, BD Biosciences #552854),
• B220-A700 (clone 16A, conjugated at WEHI)
• IgM-A647 (clone II/41, conjugated at WEHI)
• IgD-PE (clone 11-26c, conjugated at WEHI)
• isotype control IgG antibody (clone DA1E, Rabbit mAb IgG XP® Isotype Control,#3900, Cell Signaling)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Mouse primary cell isolates (in some cases propagated) were used exclusively in this study. Mouse embryonic fibroblasts and lymphoma cells from mice carrying from Myc-driven lymphoma were isolated for this study and used.

Authentication

Mouse primary cells were isolated from mice and used at an early passage number. RNA-sequencing experiment confirmed mouse mRNA exclusively in the samples. Cell isolated from genetically modified mice were genotyped by PCR.

Mycoplasma contamination

All cell isolates tested negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals

Laboratory mice of the strains: C57BL/6, B6(Cg)-Tyrc-2J/J (B6-albino) were 6 to 8 weeks old. Mid-gestation embryos were used as the source of cells from the following strains of mice Moz-lox/lox;Rosa26-CreERT2, Eμ-Myc transgenic mice, Ink4a-Arf–/–, and p53–/– . Two day old Zebrafish Tg(TO-krasG12V) and Tg(lfabp10:RFP;elaA:EGFP) were used, as described in the Methods section, main text and figure legends.

Wild animals

No wild animals were used.

Field-collected samples

No field collected samples were used.

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	Tissues were processed and erythrocytes lysed as described in reference 11. WBC counts were obtained using a Countess® Automated Cell Counter (ThermoFisher) for spleen and bone marrow and blood counts using the Advia 3120 analyzer (Bayer) .
Instrument	BD Biosciences Fortessa and LSRII were used.
Software	Data were analysed using FlowJo 10.3 (Treestar Inc.).
Cell population abundance	Cell populations were not sorted. Flow cytometric analysis was performed as described in the methods section.
Gating strategy	The gating strategy used in flow cytometry is shown in the Supplementary Data Section. Fluorescence minus one (FMO) controls, compared to unstained cells, were used to define negative cell populations and set gates for analysis.

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