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Corresponding author(s): NCOMMS-23-59502-T

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Reporting Summary

Nature Portfolio 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 Portfolio 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	All the FACS data was collected with FACSdiva 8.0 (BD Bioscience). Colony formation assay images were captured using STEMvision Stem Cell Technologies. Immunoblots and nucleic acid gels were captured using Image Lab 6.1 (BioRad). qRT-PCR data was collected with thermocycler software (Applied Biosystems).
Data analysis	Numerical data was first processed with Microsoft Excel 2016 and then analyzed and plotted with Graphpad Prism v9. All FACS data were analyzed with FlowJo 10.8 and FACSDiva on PC. All p-values and graphs were generated with GraphPad Prism 9. We used Image J software (1.46R) to quantify DNA and protein band intensity. RNA-sequencing reads were mapped using HISAT2 (version 2.0.0-beta). Adobe Illustrator CC v27.5 were used for downstream image analysis and illustration.

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 Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data that support the findings of this study are available from the corresponding author upon request. The RNA sequencing data generated in this study has been deposited at NCBI's GEO repository with accession number GSE250372. Mus musculus mm10 genome was used for annotation. RNA-sequencing data of AML patients were downloaded from The Cancer Genome Atlas via cBioPortal (cbioportal.org) and BEAT AML (Vizome, http://www.vizome.org/aml/). Published microarray data of patients with AML along with healthy controls were downloaded from GSE35008 and GSE35010. Alliance AML patient response to treatment and TNFAIP3 expression were obtained from the Alliance Statistics and Data Management Center

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Patient-derived xenograft cells were previously obtained from both males and females with diverse race and ethnicities. For detailed information, refer Supplementary Table 5.
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	All relevant clinical characteristics of patients such as diagnosis, mutational status, treatment history, response to therapy, etc. are provided in Supplementary Table 5.
Recruitment	Previously generated PDX models were obtained from the Humanized Mouse Resource of the Cancer & Blood Diseases Institute (CBDI) at Cincinnati Children's Hospital Medical Center. All participants gave written informed consent in accordance with the Declaration of Helsinki.
Ethics oversight	The Cincinnati Children's Hospital Medical Center

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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	Mouse experiments were planned in an effort to provide 60%-80% power for a target effect size of 1.2-1.5 (effect size=|mean difference|/SD). For all other experiments, at least 3 biological replicates were performed/utilized in the sample calculation.
Data exclusions	No data were excluded.
Replication	All mouse experiments used both male and female mice. Based on our extensive experience, xenograft experiments were performed using >5 recipients per condition to detect 65% relative treatment differences with 80% power at a significance level of 0.05. All in vitro/ex vivo experiments have both biological and technical replicates and be repeated multiple times. In the manuscript, n represents the number of samples/animals per experiment (each experiment being representative of at least three independent experiments). All results are expressed as means with error bars reflecting standard error of the mean (unless otherwise specified). Differences between two groups were assessed using unpaired two-tailed Student's t-tests. Replication in three independent experiments were performed to ensure reproducibility. To ensure proper tests were performed (e.g., Student's t-test, one-way ANOVA, two-way ANOVA, log-rank tests, etc.), a full-time statistician within our division was consulted.
Randomization	Animals of the same age and gender were randomly assigned to experimental groups
Blinding	No blinding was performed, as genotyping and treatments were necessary for all the experiments.

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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[ ]	[x] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used

For western blotting:
GAPDH Cell Signaling, Cat No. 5174
Vinculin Cell Signaling, Cat No. 13901
IKKbeta Cell Signaling, Cat No. 2370
phospho-IKKbeta/alpha Cell Signaling, Cat No. 2697
p65 Cell Signaling, Cat No. 8242
phospho-p65 Cell Signaling, Cat No. 3033
A20 Cell Signaling, Cat No. 5630
MLKL Abcam, Cat No. ab172868
phospho-MLKL Abcam, Cat No. ab196436
RIPK1 Cell Signaling, Cat No. 3493
phospho-RIPK1 Cell Signaling, Cat. No 31122
RIPK3 Abcam, Cat No. ab56164
phospho-RIPK3 Abcam, Cat No. ab222320
Caspase-3 Cell Signaling, Cat No. 9665
peroxidase-conjugated AffiniPure goat anti-rabbit IgG Jackson ImmunoResearch Laboratories, Cat No.111-035-003
peroxidase-conjugated AffiniPure goat anti-mouse IgG Jackson ImmunoResearch Laboratories, Cat No. 115-035-003

For flow cytometry:
Annexin V and 7AAD Cell Death Detection kit BD Pharmingen, Cat No. 559763

Validation

All western blot antibodies used have been previously reported and validated. All flow cytometry antibodies were previously reported and validated by comparing their staining pattern on BM cells by FACS, and also validated by the source company.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

MOLT16, F36P, SET2, OCIAML2, and OCIAML3 cells were purchased from DSMZ. MOLM13 were purchased from AddexBio. TF1 cells were purchased from ATCC. MOLM14 (N Shah Lab, UCSF), MV4;11 (HL Grimes Lab, CCHMC), 293T (S. Wells lab, CCHMC), CD34+ MLL-AF9;FLT3-ITD (J Mulloy Lab, CCHMC), HL60 and THP1 (A. Karsan, UBC) were gifts from other labs.

Authentication

STR loci analysis was performed on all cell lines when received and after experimentation was complete.

Mycoplasma contamination

All cell lines are routinely tested and are confirmed to be negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

We did not use commonly misidentified lines.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals

All mice were bred, housed, and handled in the Association for Assessment and Accreditation of Laboratory Animal Care-accredited animal facility of Cincinnati Children's Hospital Medical. 6-10 week old male and female BoyJ mice (Cat no. 002014, Jackson

	Laboratory) were used for all BM transplant experiments. Mice were housed at the vivarium at Cincinnati Children's Hospital Medical Center under a 14h light: 10h darkness schedule, 30-70% humidity and at 22.2±1.1ºC. All animal experiments followed all relevant guidelines and regulations and were approved by the Animal Care Committee of Cincinnati Children's Hospital Medical Center. A20Rosa Cre-ER mice were a gift from A. Ma (UCSF) and Rip3-/- (B6.129-Ripk3tm1.1Fkmc/J) were purchased from The Jackson Laboratory (Cat No. 030284).
Wild animals	N/A
Reporting on sex	Animals of both genders (male and female) were always included and randomly assigned to experimental groups. For xenograft studies, only female recipient mice were used as engraftment is superior.
Field-collected samples	N/A
Ethics oversight	All experiments were performed according to the animal guidelines upon approval of the Institutional Animal Care and Use Committee at CCHMC (IACUC2019-0072).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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	Mice were euthanized using CO2 followed by cervical dislocation. PB was collected into EDTA-coated tubes (Cat no. 22030403, Fisher Scientific), and hind limb bones (femurs, and tibias) were obtained immediately after euthanasia and stored in cold FACS buffer (1% FBS in DPBS) under sterile conditions. Bones were crushed using a mortar and pestle and then passed through a 40-µm cell strainer (Cat no. 542040, Greiner Bio-one). Primary bone marrow (BM) or peripheral blood (PB) cells were then filtered through a cell strainer (70 µm) to obtain a single-cell suspension. For analysis of cell death markers, cells were washed once with 1X PBS (GE Healthcare Life Sciences), and subsequently stained with conjugated antibodies in FACS buffer (1% FBS in DPBS) according to the manufacturer's recommendations.
Instrument	BD FACSCanto
Software	BD Facs Diva Software 8 and FlowJo 10.8
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	In all experiments, debris were excluded by using Forward scatter/Side scatter (FSC/SSC). Doublets were excluded by double forward (FSC-A and FSC-W), and side scatter (SSC-A and SSC-H). Cell death markers were analyzed using Annexin V and 7AAD staining. Double negative cells were considered live, while Annexin V positive and double positive cells were assigned as dying and dead. For analysis of eGFP expression, the same workflow was followed, excepting the cell death marker staining. Positive gates were set with signal above 10^3.

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