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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

Based on previous experience with the Eμ-myc transgenic mouse lymphoma model, sample sizes typically reflect three to five individual primary tumors as independent biological replicates. For assessing long-term outcome after in vivo-treatments, six or more tumor-bearing animals per arm were used.

2. Data exclusions

Describe any data exclusions.

No data were excluded, all probes/animals that met proper experimental conditions were included in the analysis.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experimental findings were reliably reproduced.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

No randomization was used to allocate experimental groups.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

No blinding was used during allocation of experimental groups.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	The data were analyzed by Microsoft Office Excel 2013 or Prism GraphPad 5. The limiting dilution tumor initiation data were analyzed by ELDA software (http://bioinf.wehi.edu.au/software/elda/). The gene enrichment analysis was performed using GSEA v2.0 software (http://www.broad.mit.edu/gsea). The global proteome processing was aided by using Chronos software package (Axel Semrau) and data analyzed using MaxQuant software version 1.2.2.5 (Ref. 53) and R-statistical software (https://www.r-project.org/).

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	No restrictions on reagent availibility

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	Antibodies against total ?-catenin (BD Biosciences, cat. no. 610153, 1:200, species reactivity: Hu (QC testing), M, R, D; application: WB (routinely tested), ICH, IP, IF (tested during development)), active ?-catenin (dephosphorylated at serine 37 [Ser37] and threonine 41 [Thr41]; Millipore, cat. no. 05-665, 1:1000, species reactivity: Hu, M, R; application: FC, ICC, IHC, IH(P), WB), H3K9me3 (Abcam, ab8898, 1:2,000, species reactivity: mammal, S. cerevisae, X. laevis, D. melanogaster; tested for applications: IHC, ICC, WB, FC, ChIP, ChIPseq), total Erk (Cell Signaling Technology [CST], cat. no. 9102, 1:1000, species reactivity: Hu, M, R, H, Monkey, Mink, Zebrafish, Bovine, Pig, S. cerevisiae; tested application: WB, IP, ICH), phospho-Erk1/2 (i.e. Erk1/2-P-Thr202/Tyr204; CST, cat. no. 4376, 1:1000, species reactivity: Hu, M, R, Hm, Monkey, Mink, Zebrafish, Pig, S. cerevisiae; tested application: WB, IP, ICH), total Akt (CST, cat. no. 9272, 1:1000, species reactivity: Hu, M, R, Hm, Monkey, Mink, Zebrafish, Bovine, Pig, S. cerevisiae; tested application: WB, IP, ICH, FC), phospho-Akt (i.e. Akt-P-Ser473; CST, cat. no. 4060, 1:2000, species reactivity: H, M, R, Monkey; tested application: WB, IP, ICH, IF, FC), total GSK3? (CST, cat. no. 12456, 1:1000, species reactivity: H, M, R, Monkey; tested application: WB, IP, ICH, IF, FC), phospho-GSK3? (i.e. GSK3?-P-Ser9; CST, cat. no. 5558, 1:1000, species reactivity: Hu, M, R, Hm; tested application: WB, IP, IF, FC) and α-Tubulin (Sigma, T5168, 1:1000, species reactivity: Hu, M, R, Monkey, Chicken, Kangaroo, Sea Urchin; tested application: WB, RIA, IF) were used in this study.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

Human cancer cell lines were obtained from DSMZ (Leibniz-Institut Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH), ATCC or Biomol: RCK8 (DSMZ-No. ACC-561), Eheb (DSMZ-No. ACC-67), K562 (DSMZ-No. ACC-10), Mec1 (DSMZ-No. ACC-497), Molm13 (DSMZ-No. ACC-554), SW480 (DSMZ-No. ACC-313), LS174T (DSMZ-No. ACC-759), DLD-1 (DSMZ-No. ACC-278), Caco-2 (DSMZ-No. ACC-169), SKMel28 (ATCC No. HTB-72), MeWo (ATCC No. HTB-65), WM266.4 (Biomol No. WM266-4-01). Omm2.3 cells were kindly provided by Martina J. Jager.

b. Describe the method of cell line authentication used.

The cell lines bought within last 4 years were not additionally authenticated (RCK8, Eheb, Mec-1, purchased at DSMZ in December 2013, authentication by nanoplex PCR of short tandem repeat markers provided by the distributor). All other cell lines were authenticated by DSMZ using SNP-based multiplex approach in October 2017. SNP profiles matched known profiles or were unique.

c. Report whether the cell lines were tested for mycoplasma contamination.

The cell lines regularly tested for mycoplasma contamination.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

None of the cell lines used are listed in the ICLAC list.

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

6–8-week-old C57BL/6 (“wild type”) female mice were used as recipients for in vivo lymphoma or leukemia propagation.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

The tumor biopsies from five B-cell leukemia patients (age 60-72 years, all male, initial diagnosis or relapse biopsies), five diffuse large B-cell lymphoma [DLBCL] patients (age 49-77 years, three females and two males, matched pairs of initial diagnosis and relapse biopsies) and acute myeloid leukemia [AML] patients (age 33-83 years, four females and one male, initial diagnosis) were used in this study.

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Flow Cytometry Reporting Summary

Form fields will expand as needed. Please do not leave fields blank.

Data presentation

For all flow cytometry data, confirm that:

☒ 1. The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ 2. 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).

☒ 3. All plots are contour plots with outliers or pseudocolor plots.

☒ 4. A numerical value for number of cells or percentage (with statistics) is provided.

Methodological details

5. Describe the sample preparation.	Please see Methods, Generation of primary lymphomas and leukemias, page 19
6. Identify the instrument used for data collection.	The data were acquired using FACS Calibur™ (BD Biosciences) or ImageStream®X Mark II (AMNIS®, Merck Millipore). The sample sorting was performed using FACS Aria II (BD Biosciences).
7. Describe the software used to collect and analyze the flow cytometry data.	Data acquired by FACS Calibur™ was analyzed using BD CellQuest™ Pro Software (BD Biosciences). Data acquired by ImageStream®X was analyzed using IDEAS® Software (AMNIS®). FACS sorting data was assessed using FACS Diva™ Software (BD Biosciences).
8. Describe the abundance of the relevant cell populations within post-sort fractions.	Representative figures provided in Extended Data Figure 10a.
9. Describe the gating strategy used.	For cell sorting, the first gate was set to "viable" cells in FSC/SSC plot, and from those populations of interest were gated in "green vs red" plot (B525/YG582). Positive and negative cell fractions were clearly separable (see Extended Data Figure 10a).

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