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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.

No statistical test was used to determine sample size and sample size was chosen based on literature.

2. Data exclusions

Describe any data exclusions.

No inclusion or exclusion criteria were used for samples or animals

3. Replication

Describe whether the experimental findings were reliably reproduced.

Attempts at replication were successful

4. Randomization

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

Biochemical and in vitro experiments did not need randomization, so this was not part of experimental design. In in vivo experiments utilizing mice, we randomly selected mice for subcutaneous injection.

5. Blinding

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

The investigators were not blinded to allocation during experiments and outcome assessment. Blinding was not necessary as we used objective quantitative assays to generate the data.

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.	RNA-seq reads were mapped and analyzed with a custom bioinformatic pipeline based on STAR, SAMTOOLS, and the R packages DEGseq and DEseq2. GO analyses were performed using version 6.8 of the DAVID web server. CHIP-seq FASTQ files were mapped with bowtie2 (v2.1.0). GenePattern 2.0 was used to analyze Microarray data. Integrative Genome Viewer (IGV2.3) was used to visualize microarray and CHIP-seq data. Mutual exclusivity was performed with Weighted Exclusivity Test (WExT) software. T-test, ANOVA, Mantel-Cox and Pearson Correlation Coefficient analysis were performed in Prism6. Image J was used for band quantification. FlowJo software and Attune NxT Flow Cytometer software were used for flow cytometry analysis. SEQUEST was used for protein identification in mass spectrometry. DTASelect and CONTRAST were used to assemble SEQUEST identifications from multiple experiments.

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.	All relevant materials are available from the authors

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	All antibodies were used at a dilution of 1:1000 unless specified. The following antibodies were used: anti-FLAG (Sigma, F7425,1:3000), anti-HA (Biolegend, #901513), anti-Cullin1 (Invitrogen, #71-8700), anti-Cullin3 (Bethyl Laboratories, A301-109A), anti-ubiquitin K48 (EMD Millipore, 05-1307), anti-Roquin1/2 (EMD Millipore, MABF288), anti-Roquin2(Santa Cruz, sc-165026) anti-Roquin2(Bethyl Laboratories, A305-150A) anti-KLHL6 (Abcam, ab182163), anti-KLHL6(Novus Biologicals, NBP1-46128) anti-Tubulin(Santa Cruz, sc-8035), anti-GAPDH(EMD Millipore, MAB374,1:5000), anti-CDK1(Santa Cruz, sc-954), anti-CDK2(Santa Cruz, sc-163), anti-p-AKT S473 (Cell Signaling Technology, #4051), anti-p-ERK T202/Y204 (Cell Signaling Technology, #9101), anti-ERK1/2 (Cell Signaling Technology, #9102), anti-AKT (Cell Signaling Technology, #4691), anti-TNFAIP3(Cell Signaling Technology, #5630), anti-p-IkB S32 (Cell Signaling Technology, #2859,1:500), anti-p100/p52(Cell Signaling Technology, #4882), anti-p105/p50(Santa Cruz, sc-7178), anti-RelA(Santa Cruz, sc-372), anti-RelB(Santa Cruz, sc-226), anti-histone H2A(EMD Millipore, 07-146) and anti-histone H3(Abcam, ab1791,1:5000), ECL Rabbit IgG HRP-linked whole antibody(GE healthcare, NA934-1ML,1:5000), ECL Mouse IgG, HRP-linked whole antibody(GE healthcare, NA931-1ML,1:5000), Anti-Rat IgG (H+L) polyclonal antibody(Jackson Immunoresearch, 112-035-003,1:5000), Anti-Goat IgG (H+L) polyclonal antibody(Jackson Immunoresearch, 705-035-003,1:5000). KLHL6, Roquin1/2, TNFAIP3, CULLIN1, CULLIN3, p100/p52, p105/p50 and RelA antibodies were validated in our lab utilizing RNAi as well as overexpression, and were also validated by manufacturer. All other primary antibodies were validated on manufacturer datasheets. The following agarose beads were used: anti-FLAG-M2 affinity gel (Sigma, A2220) and Strep-Tactin Superflow 50% suspension (Neuromics).

10. Eukaryotic cell lines

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

HEK293T were purchased from ATCC. DLBCL cell lines were kindly provided by Dr. Andrei Thomas-Tikhonenko, Dr. Yibin Yang, and Dr. Laura Pasqualucci

b. Describe the method of cell line authentication used.

Authentication was not performed as cells were not listed in the commonly misidentified category.

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

All cell lines were free of mycoplasma contamination (tested by MycoAlert kit, Lonza).

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.

No commonly misidentified cell lines were used

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.

Mus musculus, NOD/SCID/IL2Rγ−/− (NSG), male and 12 weeks.

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 study did not involve human subjects.

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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.	DLBCL cell lines were kindly provided by Dr. Andrei Thomas-Tikhonenko, Dr. Yibin Yang, and Dr. Laura Pasqualucci. For GFP expressing cells, samples were resuspended in PBS and analyzed. Other stainings were performed on live cells according to manufacturer's protocol.
6. Identify the instrument used for data collection.	Attune NxT Flow Cytometer and BD Accuri C6.
7. Describe the software used to collect and analyze the flow cytometry data.	Attune NxT Flow Cytometer software and Flowjo was used to collect the data
8. Describe the abundance of the relevant cell populations within post-sort fractions.	For GFP positive-sorted cells, the purity was determined by the percentage of GFP cells during sorting. All the other samples were pure population as they were DLBCL cell lines, not primary cell lines.
9. Describe the gating strategy used.	- For Fig3c and 7j: Positive GFP control: GFP expressing cells. Negative GFP control: non-infected cells. Gate was applied excluding the GFP-negative cells and including the GFP-positive cells only. For AnnexinV staining, positive AnnexinV was defined for cells incubated with AnnexinV-Alex680. Negative AnnexinV control was defined for cell non-incubated with AnnexinV-Alex680 (non-stained). Statistical analysis was performed on the double positive population. -For 7i, same as above except that cells were sorted for GFP-positive cells. - For S4h: Positive GFP control: GFP expressing cells. Negative GFP control: non-infected cells. Gating was applied excluding the GFP-negative cells and including the GFP-positive cells only. - For S5a: positive control: cells incubated with primary antibody (IgM-FITC or IgG-APC). Negative control: cells incubated with no primary antibody. Graphs show stained vs non-stained cells.

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