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Reporting Summary

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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	For Proximity ligation assay, images were acquired by CellSens imaging software (Olympus) with Zeiss Axio Observer 7 microscope. For FACS, BD FACSDIVA™ SOFTWARE were used. For Western blot, images were collected by film exposure, UVP BioSpectrum 810 Imaging System or ChemiDoc MP Imaging System (BioRad). For colony forming assay, images were acquired GelCount analyzer and packages Q-Capture pro 7 connected with Olympus IX71 microscope. To determine the number of viable cells, the trypan blue exclusion method was applied, using the Countess II FL Automated Cell Counter. For in vivo bioimaging, IVIS 100 bioluminescence/optical imaging system was used. The IFITM3 protein structure was modeled by coarse-grained (CG) molecular dynamics simulation method in GROMACS (http://www.gromacs.org/) with Martini force field. The three snapshots extracted from the CG simulations were converted to an all-atom system using Martini tools. The all-atom simulations were performed using GROMACS packageand CHARMM force field, with TIP3 water model. To set up the mixed lipid bilayer with water in the upper and inner regions, CHARMM-GUI was used. For immunohistology of immunized or non-immunized spleen sections, images were acquired on a ZEISS LSL 880 confocal microscope and analyzed on ZEN 2.3 (Zeiss) software. For cell membrane stiffness, the Single-cell size-normalized acoustic scattering (SNACS) was measured by custom software coded in LabVIEW 2017 (National Instruments). A parallel volume was measured with Coulter Counter (Beckman Coulter) to quantify average cell volume.
Data analysis	For analysis of Proximity ligation assay, ImageJ, BlobFinder, Excel and GraphPad Prism 7 were used. For FACS analysis, FlowJo, SigmaPlot and GraphPad Prism 7 was used. For colony forming assay, number of colonies were counted by GelCount analyzer and analyzed by SigmaPlot. For in vivo leukemia burden analysis, GraphPad Prism 7 was used. For gene expression analysis, Excel, SigmaPlot and GraphPad Prism 7 was used. For log-rank test to compare survival differences between patient groups, R package 'survival' Version 2.35-8 and Cox proportional hazards regression model in R package for the multivariate analysis (https://www.r-project.org/) were used. Integrative Genomics Viewer (IGV) was used to visualize ChIP-seq tracks. For RNA-seq analysis raw sequence reads were mapped to the mouse genome (mm10) using STAR v2.5.39, and the frequency of genes was counted using featureCounts v1.5.110. The raw counts were then normalized using the trimmed mean of M values (TMM) method and compared using Bioconductor package "edgeR". Reads per kilo base per million (RPKM) mapped reads were also calculated from the

raw counts. For differential expression analysis, transcripts were quantified using Salmon v1.1.0 against gencode GRCm38 vM24 transcript annotations; normalisation and statistical analysis was done in R using DESeq2 v1.28.1. Differentially expressed genes were identified if RPKM ≥1 in at least one sample, fold change ≥2, and P ≤ 0.05. RPKM data were later used in the Gene set enrichment analysis. GSEA analysis was performed using the DOSE package in R12, genes were ranked by log2 fold-change, gene sets were obtained from MSigDB or from internal data as indicated.

For Bio-ID data analysis, proteins were identified from the MS raw files using Mascot search engine (Matrix science). MS/MS spectra were searched against the SwissProt human database. All searches included carbamidomethyl cysteine as a fixed modification and oxidized Met, deamidated Asn and Gln, acetylated N-term as variable modifications. Three missed tryptic cleavages were allowed. The MS1 precursor mass tolerance was set to 10 ppm and the MS2 tolerance was set to 0.6 Da. A 1% false discovery rate cutoff was applied at the peptide level. Only proteins with a minimum of two peptides above the cutoff were considered for further study. For comparison to empty vector control, background peptide abundances for missing values were imputed from a Gaussian distribution centered around the minimum observed abundance using the MinProb method from MSnbase package in R.

For proteomics, raw spectral data was analyzed using MaxQuant v1.5.1.2 to identify and quantify peptide abundance and searched against the human Swiss-Prot annotated human proteome from Uniprot (downloaded with 20,303 entries). The "match-between-runs" option was selected to increase peptide identifications while the "fast LFQ" option was selected to calculate label-free quantification values (LFQ) of identified proteins. All other settings were left to the default MaxQuant values. The MaxQuant output data was analyzed using Perseus and the R program (version 3.4.0). Proteins annotated as "reverse", "only identified by site", and "potential contaminant" were filtered out as well as proteins that were quantified in less than 2 out of 3 biological replicates in at least one experimental group. Missing values were imputed based on the normal distribution of the dataset as implemented by Perseus. Volcano plots were generated using output from a two-sample t-test comparing the log2 transformed LFQ protein abundance values from different cell lines with a false discovery rate (FDR) set to 0.01.

For phospho-proteomic analysis, 15mg total protein for each sample was digested with trypsin, and 500ug total protein for each sample was digested with LysC/trypsin for IMAC analysis. Samples were purified over C18 columns and dried in a lyophilizer. Dried samples were resuspended and enriched with Fe-IMAC beads, purified over C18 STAGE tips (Rappsilber). Replicate injections of each sample were run non-sequentially on the instrument. Peptides were eluted using 150-minute (IMAC) linear gradient of acetonitrile in 0.125% formic acid delivered at 280 nL/min. Tandem mass spectra were collected in a data-dependent manner with a Thermo Orbitrap Fusion™ Lumos™ Tribrid™ mass spectrometer using a top-twenty MS/MS method, a dynamic repeat count of one, and a repeat duration of 30 sec. Real time recalibration of mass error was performed using lock mass (Olsen) with a singly charged polysiloxane ion m/z = 371.101237. MS/MS spectra were evaluated using SEQUEST and the Core platform from Harvard University (Eng, Huttlin, Villen). Files were searched against the SwissProt Homo sapiens FASTA database. A mass accuracy of +/-5 ppm was used for precursor ions and 0.02 Da for product ions. Enzyme specificity was limited to trypsin, with at least one tryptic (K- or R-containing) terminus required per peptide and up to four mis-cleavages allowed. Cysteine carboxamidomethylation was specified as a static modification, oxidation of methionine and phosphorylation on serine, threonine, and tyrosine residues were allowed as variable modifications. Reverse decoy databases were included for all searches to estimate false discovery rates, and filtered using a 1% FDR in the Linear Discriminant module of Core. Peptides were also manually filtered using a -/+ 5ppm mass error range and presence of a phosphorylated residue. All quantitative results were generated using Skyline (MacLean) to extract the integrated peak area of the corresponding peptide assignments. Accuracy of quantitative data was ensured by manual review in Skyline or in the ion chromatogram files.

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. 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

Patient-outcome data for B-ALL were obtained from the National Cancer Institute TARGET DATA Matrix of the Children's Oncology Group (COG) Clinical Trial P9906 (GSE11877; Harvey et al., 2010; Kang et al., 2010), Eastern Cooperative Oncology Group (ECOG) Clinical Trial E2993 (GSE5314; Juric et al., 2007) and St. Jude Children's Research Hospital (https://www.stjuderesearch.org/site/data/ALL3/; Ross et al., 2003). Patient-outcome data for mantle cell lymphoma were obtained from https://llmpp.nih.gov/MCL/ 32. Patient-outcome data for AML were obtained from TCGA Acute Myeloid Leukemia Project (http://www.cbioportal.org/study/summary?id=laml_tcga_pub#clinical; Cancer Genome Atlas Research Network, 2013). Proteomics data was deposited to the ProteomeXchange Consortium via the PRIDE partner repository with following accession numbers: cell surface proteome PXD014691, phosphoproteome PXD020696 and IFITM3 interactomes PXD020697. IFITM3 mRNA levels across human normal and malignant B-lymphoid samples were obtained from http://Amazonia.transcriptome.eu/. All other data are available from the corresponding author upon reasonable request. Genome binding/occupancy profiling from WT and IKDN stromal adherent pre-B cells were obtained from GSE86897. Immunohistochemistry images for IFITM3 levels in normal or malignant B cells were obtained from The Human Protein Atlas https://www.proteinatlas.org/. ChIP–seq data of the genome wide mapping of IKZF1 binding (ChIP-Seq) in human patient-derived B-ALL xenograft cells were obtained from GSE58825. ChIP–seq data of the genetic analysis of IKZF1 target genes (ChIP-Seq) and tumor suppressor function in BCR-ABL1+ pre-B ALL were obtained from GSE90656. RNA sequencing (RNA-Seq) data with Ifitm3+/+ and Ifitm3-/- BCR-ABL1 or NRASG12D B-ALL cells are available at GSE155305. RNA sequencing (RNA-Seq) data with Ptenfl/fl pre-B cells carrying 4-OHT-inducible Cre-ERT2 or ERT2 are available at GSE155618. All other data needed to evaluate the conclusions in the paper are available within the main text or supplementary materials.

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	For in vitro experiments, phenotypic analyses including Western blot and FACS were performed in at least three independent experiments, using biological replicates. No statistical methods were used to predetermine sample size for in vitro experiments. Sample sizes were selected empirically from previous experimental experience, and/or from sizes generally employed in the field. For in vivo transplantation experiments, the minimal number of mice in each group was calculated through use of the 'cpower' function in the R/Hmisc package. The precise number of sample used in indicated in manuscript. The precise number of sample used in indicated in manuscript.
Data exclusions	No data were excluded from the analyses.For all FACS analysis, only single cells were included in further analysis. Duplets determined by FSC-H /FCS-A as well as SSC-H/SSA-A were excluded. This was done to avoid false positive events due to doublets (Kudernatsch RF et al. Cytometry A 2013, PMID 23281028).
Replication	The experimental findings were reliably reproduced using biological replicates and multiple cells indicated in manuscript.
Randomization	Samples and animals were randomly divided into experimental groups.
Blinding	Mice were randomly allocated to groups by investigators who did not participate in any subsequent analysis. The performers of the mouse experiments (injections, drug treatments) were blinded to the randomization process.

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

Antibodies for Western blot
Polyclonal anti-STAT1-pY701 Cell Signaling Technology Cat# 9172 (1:1000)
Polyclonal anti-STAT1 Cell Signaling Technology Cat# 5605 (1:1000)
Polyclonal anti-STAT5-pY694 Cell Signaling Technology Cat# 9351 (1:1000)
Polyclonal anti-STAT5 Cell Signaling Technology Cat# 9363 (1:1000)
Polyclonal anti-IFITM3 Cell Signaling Technology Cat# 9037 (1:1000)
Polyclonal anti-AKT-pS473 Cell Signaling Technology Cat# 9271 (1:750)
Polyclonal anti-AKT Cell Signaling Technology Cat# 9272 (1:1000)
Polyclonal anti-ERK-pT202/Y204 Cell Signaling Technology Cat# 4370 (1:1000)
Polyclonal anti-ERK Cell Signaling Technology Cat# 9102 (1:1000)
Polyclonal (D8E8G) anti-IFITM3 Cell Signaling Technology Cat# 59212 (1:1000)
Polyclonal (D84C12) anti-c-Myc Cell Signaling Technology Cat# 5605 (1:1000)
Polyclonal anti-c-Abl-pY412 Cell Signaling Technology Cat# 2865 (1:1000)
Polyclonal anti-c-Abl Santa Cruz Biotechnology Cat# sc-131 (1:1000)
Polyclonal anti-Src-pY416 Cell Signaling Technology Cat# 6943 (1:1000)
Polyclonal anti-Lyn Cell Signaling Technology Cat# 2796 (1:1000)

Polyclonal anti-Syk-pY352 Cell Signaling Technology Cat# 2717 (1:1000)
Polyclonal anti-Syk Cell Signaling Technology Cat# 2712 (1:1000)
Polyclonal (C-2) anti-Bcl-2 Santa Cruz Biotechnology Cat# sc-7382 (1:1000)
Polyclonal anti-p21 (C-19) Santa Cruz Biotechnology Cat# sc-397 (1:1000)
Polyclonal anti-CD19-pY531 Cell Signaling Technology Cat# 3571 (1:1000)
Monoclonal (D4V4B) anti-CD19 Cell Signaling Technology Cat# 90176 (1:1000)
Monoclonal (1C12) anti-p53 Cell Signaling Technology Cat# 2524 (1:1000)
Polyclonal anti-p19/Arf ABCAM Cat# ab80 (1:1000)
Monoclonal (4G10) anti-Phosphotyrosine EMD Millipore Cat# 05-321 (1:1000)
Polyclonal anti-HA tag ABCAM Cat# ab9110 (1:1000)
Polyclonal (D6N9Y) anti-IKZF1 Cell Signaling Technology Cat# 14859 (1:1000)
Polyclonal anti-PIK3CD; p110δ ABCAM Cat# ab109006 (1:1000)
Monoclonal (M2) anti-FLAG Sigma-Aldrich Cat# F1804 (1:1000)
Polyclonal anti-eIF4E Santa Cruz Biotechnology Cat# sc-13963 (1:1000)
Polyclonal anti-LYN-pY397 Cell Signaling Technology Cat# 70926 (1:1000)
Monoclonal (108D2) anti-p70 S6K-pT389 Cell Signaling Technology Cat# 9234 (1:1000)
Polyclonal anti-p70 S6K-pT421/S424 Cell Signaling Technology Cat# 9204 (1:1000)
Monoclonal (49D7) anti-p70 S6 Kinase Cell Signaling Technology Cat# 2708 (1:1000)
Monoclonal (D30A3) anti-RICTOR-pT1135 Cell Signaling Technology Cat# 3806 (1:1000)
Monoclonal (53A2) anti-RICTOR Cell Signaling Technology Cat# 2114 (1:1000)
Polyclonal anti-CXCR4-pS339 Cell Signaling Technology Cat# 59028 (1:1000)
Polyclonal anti-CXCR4 Novus Biologicals Cat# 74396 (1:1000)
Polyclonal anti-FAK-pY397 Cell Signaling Technology Cat# 3283 (1:1000)
Polyclonal anti-FAK-pY575/577 Cell Signaling Technology Cat# 3281 (1:1000)
Monoclonal (D2R2E) anti-FAK Cell Signaling Technology Cat# 13009 (1:1000)
Polyclonal anti-PAK1-pS199/204 Cell Signaling Technology Cat# 2605 (1:1000)
Polyclonal anti-PAK1 Cell Signaling Technology Cat# 2602 (1:1000)
Polyclonal anti-ITGB1-pY783 ABCAM Cat# ab62337 (1:1000)
Polyclonal anti-ITGB1-pT788/789 Thermo Fisher Scientific Cat# 44-872G (1:1000)
Polyclonal anti-ITGB1 Cell Signaling Technology Cat# 4706 (1:1000)
Monoclonal (C4) anti-β-actin Santa Cruz Biotechnology Cat# sc-47778 (1:5000)

Antibodies for FACS
Monoclonal (HIB19) anti-human CD19 Biolegend Cat# 302254 (1:50)
Monoclonal (M2) anti-FLAG Columbia Biosciences Cat# M2 (1:200)
Polyclonal anti-HA tag Columbia Biosciences Cat# D5-1718 (1:200)
Monoclonal (OKT4) anti-human CD4 Biolegend Cat# 317418 (1:50)
Monoclonal (UCHT1) anti-human CD3 Biolegend Cat# 555335 (1:50)
Monoclonal (G20-127) anti-human IgM BD Biosciences Cat# 561285 (1:50)
Monoclonal (6D5) anti-mouse CD19 Biolegend Cat# 115508 (1:200)
Monoclonal (RA3-6B2) anti-B220 (CD45R) Biolegend Cat# 103224 (1:200)
Monoclonal (HM79-12) anti-CD79b Biolegend Cat# 132804 (1:200)
Monoclonal (RB6-8C5) anti-mouse Gr-1 (Ly-6GC) Biolegend Cat# 108422 (1:200)
Monoclonal (PK136) anti-mouse NK-1.1 Biolegend Cat# 108730 (1:200)
Monoclonal (2B8) anti-CD117 (c-kit) Biolegend Cat# 105808 (1:200)
Monoclonal (D7) anti-Sca-1 (Ly-6A/E) Biolegend Cat# 108102 (1:200)
Monoclonal (S11) anti-mouse CD43 Biolegend Cat# 143208 (1:200)
Monoclonal (6C3) anti-mouse BP-1 (Ly-51) Biolegend Cat# 108308 (1:200)
Monoclonal (M1/69) anti-mouse CD24 Biolegend Cat# 101822 (1:200)
Monoclonal (R6-60.2) anti-mouse IgM BD Biosciences Cat# 553408 (1:200)
Monoclonal (11-26c.2a) anti-mouse IgD Biolegend Cat# 405716 (1:200)
Monoclonal (B3B4) anti-mouse CD23 BD Biosciences Cat# 561773 (1:200)
Monoclonal (7E9) anti-mouse CD21/CD35 Biolegend Cat# 123412 (1:200)
Monoclonal (M1/70) anti-mouse Mac-1 (CD11b) Biolegend Cat# 101206 (1:200)
Monoclonal (53-7.3) anti-mouse CD5 Biolegend Cat# 100612 (1:200)
Monoclonal (17A2) anti-mouse CD3 Biolegend Cat# 100204 (1:200)
Monoclonal (RM4-5) anti-mouse CD4 BD Biosciences Cat# 553051 (1:200)
Monoclonal (Jo2) anti-mouse CD95 BD Biosciences Cat# 562499 (1:200)
Monoclonal (GL7) anti-mouse GL7 Affymetrix eBioscience Cat# 13-5902-82 (1:200)
Monoclonal (L276F12) anti-mouse CXCR4 Biolegend Cat# 146508 (1:200)
Monoclonal (GL-1) anti-mouse CD86 Biolegend Cat# 105016 (1:200)
Monoclonal (A7R34) anti-mouse CD127 (IL-7R) eBioscience Cat# 135012 (1:200)
Monoclonal (OX-7) anti-mouse Thy1 (CD90) BD Biosciences Cat# 551401 (1:200)
Monoclonal (RM2-5) anti-mouse CD2 Biolegend Cat# 100108 (1:200)

Monoclonal (HM48-1) anti-mouse CD48 Biolegend Cat# 103415 (1:200)
Monoclonal (IM7) anti-mouse CD44 Biolegend Cat# 103012 (1:200)
Monoclonal (MEC13.3) anti-mouse Pecam1 Biolegend Cat# 102508 (1:200)
Monoclonal (TY/23) anti-mouse CD73 (5NTD) BD Biosciences Cat# 550741 (1:200)
Monoclonal (37.51) anti-mouse CD28 BD Biosciences Cat# 553297 (1:200)
Monoclonal (4G2) anti-mouse CD319 Biolegend Cat# 152004 (1:200)
Monoclonal (OX-97) anti-mouse CD22 Biolegend Cat# 126112 (1:200)
Polyclonal anti-GLUT3 Alomone labs Cat# AGT-023 (1:200)
Monoclonal (93) anti-mouse CD16/32 Biolegend Cat# 101314 (1:200)
Monoclonal (2G10) anti-CIP2A Novus Biologicals Cat#59722APC (1:200)
Monoclonal (SA15-21) anti-mouse TLR4 (CD284) Biolegend Cat# 145404 (1:200)
Polyclonal anti-KV1.3 (KCNA3) Alomone labs Cat# APC-101 (1:200)
Polyclonal anti-Insulin R/CD220 R&D Systems Cat# FAB1544A (1:200)
Monoclonal (P84) anti-mouse CD172a (SIRPα) Biolegend Cat# 144014 (1:200)
Polyclonal anti-ABCG1 Invitrogen Cat# PA5-72939 (1:200)
monoclonal (EPR13130) anti-TMEM173 ABCAM Cat# ab208874 (1:200)
Polyclonal anti-ORP8 (OSBPL8) Biorbyt Cat# orb496769 (1:200)
Polyclonal anti-OSBPL5 Biorbyt Cat# orb189989 (1:200)
Polyclonal anti-Squalene Epoxidase Biorbyt Cat# orb7410 (1:200)
Monoclonal (22H9) anti-mouse TSLPR (TSLP-R) Biolegend Cat# 151806 (1:200)
Monoclonal (MAb-CC1) anti-mouse Ceacam1 (CD66a) Biolegend Cat# 134524 (1:200)
Monoclonal (AA4.1) anti-mouse CD93 Biolegend Cat# 136504 (1:200)
Monoclonal (L276F12) anti-mouse CD184 (CXCR4) Biolegend Cat# 146508 (1:200)
Monoclonal (A7R34) anti-mouse CD127 (IL-7Rα) Biolegend Cat# 135012 (1:200)
Monoclonal (PC61) anti-CD25 Biolegend Cat# 102008 (1:200)
Monoclonal (K10.6) anti-mouse CD72 a, b and d BD Biosciences Cat# 550966 (1:200)
Monoclonal (mCD44.7) anti-mouse CD84 Biolegend Cat# 122806 (1:200)
Brilliant Violet 421™ Streptavidin Biolegend Cat# 405225 (1:200)
Monoclonal (5H10-27(MFR5)) anti-mouse CD49e (Integrin α5) Biolegend Cat# 103805 (1:200)
Monoclonal (GoH3) anti-mouse CD49f (Integrin α6) Biolegend Cat# 313612 (1:200)
Monoclonal (MEL-14) anti-mouse CD62L (L-selectin) Biolegend Cat# 104408 (1:200)
Monoclonal (HMβ1-1) anti-mouse CD29 (Integrin β1) Biolegend Cat# 102216 (1:200)
Monoclonal (37.51) anti-mouse CD28 BD Biosciences Cat# 553297 (1:200)
Monoclonal (SA275A11) anti-mouse CD20 Biolegend Cat# 150410 (1:200)
Anti Ct-B (Cholera toxin subunit B) antibody Thermo Fisher Scientific Cat# V34405 (1:200)

Antibodies for PLA
Polyclonal anti-human IgM OriGene Cat# AP10433PU-N (1:150)
Polyclonal anti-human LAMP1 R & D Systems Cat# IC7985G (1:150)
Polyclonal (D8E8G) anti-IFITM3 Cell Signaling Technology Cat# 59212 (1:150)
Monoclonal (CB3-1) anti-CD79B Thermo Fisher Scientific Cat# 14-0793-82 (1:150)

Antibodies for immunofluorescence, Immunization
Biotinylated Peanut Agglutinin (PNA) Vector Laboratories Cat# B-1075 (1:200)
Alexa Fluor® 647 Streptavidin Biolegend Cat# 405237 (1:200)
Polyclonal (RA3-6B2) anti-B220 BD Biosciences Cat# 553089 (1:200)
Monoclonal (17A2) anti-mouse CD3 Biolegend Cat# 100214 (1:200)

Antibody for lipid strip
Polyclonal anti-GST tag Thermo Fisher Scientific Cat# CAB4169 (1:1000)
Monoclonal (D5A7) anti-Biotin Cell Signaling Technology Cat# 5597 (1:1000)

Antibodies for cell stimulation.
(For the Measurement of intracellular calcium mobilization, 10 µg ml-1 of antibodies were added to 1 × 106 viable cells. For the In vitro crosslinking, 2.5 µg ml-1 of antibodies were added to 1 × 106 viable cells.)
Polyclonal anti-HA tag ABCAM Cat# ab9110
Monoclonal (1D3) purified NA/LE anti-mouse CD19 BD Biosciences Cat# 553782
Polyclonal anti-mouse IgM Southern Biotech Cat# 1020-01
Polyclonal anti-human IFITM3 Bioss Cat# bs-12265R
Polyclonal F(ab')2 anti-human µ chain Jackson Immunoresearch Cat# 109-006-129
Monoclonal (OKT3) purified LE/AF anti-human CD3 Biolegend Cat# 317304

Validation

All antibodies are commercially available and validated by the manufactures for the applications and species used in this study.

See manufactures websites for validation statements (www.abcam.com; www.cellsignal.com; https://www.bdbiosciences.com/en-us; h ttps://www.biolegend.com; https://www.thermofisher.com; https://www.scbt.com; https://www.novusbio.com/; https://www.emdmillipore.com; https://www.sigmaaldrich.com; https://columbiabiosciences.com; https://www.alomone.com; https://www.rndsystems.com; https://www.biorbyt.com; https://www.origene.com

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	BV-173 Ph+ ALL carrying BCR-ABL1, MAP3K14 and IKZF1 lesions from DSMZ. JEKO1 Mantle cell lymphoma carrying IGH-CCND1, ITK, MAP2K1 and TP53 lesions from ATCC. Jurkat T-ALL carrying PTEN, LCK and CD4 lesions from ATCC. Detail information for patient-derived samples used are listed in Supplementary table 7 and 8. HEK293FT cells were used for generation of retroviruses and lentiviruses (see Methods).
Authentication	Patient-derived cells or cell lines used in this study (see Supplementary tables 7 and 8) and HEK293FT cells were validated by STR DNA profiling analysis.
Mycoplasma contamination	The cell line tested negative for mycoplasma contamination by PCR analysis.
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	All mouse models used in the study are listed in Supplementary Table S9. NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) were purchased from Jackson Laboratory. Ifitm3tm1Masu from Dr. Michael S. Diamond were backcrossed to C57BL/6J background for more than 8 generations. B6.C(Cg)-Cd79atm1(cre)Reth/EhobJ (Mb1-Cre) were purchased from Jackson Laboratory. B6.129S2-Ighmtm1Cgn/J (muMT mice) were purchased from Jackson Laboratory. C;129S4-Ptentm1Hwu/J (Ptenfl/fl) were purchased from Jackson Laboratory. To generate a model for pre-leukemic B cell precursors expressing BCR-ABL1, LSL-Bcr+/ BCR-ABL1 mice were crossed with Mb1-Cre strain (Mb1-Cre x LSL-Bcr+/ BCR-ABL1) for excision of a stop-cassette in early pre-B cells. For in vivo oncogenic priming assay with Mb1-Cre x LSL-Bcr+/ BCR-ABL1 B-cell precursors, 8- to 10-week-old female NSG mice were randomly allocated before injection. For animals bred in house, littermates of the same sex were randomized to experimental groups. For in vivo leukemia initiation assay 8- to 10-week-old female NSG mice were randomly allocated before injection. All mouse experiments were subject to institutional approval by the Beckman Research Institute of City of Hope Animal Care and Use Committee. Temperatures of 18-23°C with 40-60% humidity were maintained with 14-hour light/10-hour dark cycle. Following score was considered as end-point. 1. Failure to eat food / drink water for 24 hours. 2. Failure to make normal postural adjustments / display normal behavior. 3. Tumor Burden (1.5 cm X 1.5c,X1.5 cm, tumor ulceration is NOT expected). If an animal either loses 25% of the initial body weight (or reaches 16g of body weight, regardless of the initial weight) or if we observe a weight loss of 15% on two sequential weight measurements, we euthanized the mouse immediately.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the fields.
Ethics oversight	All mouse breeding experiments were subject to institutional approval by by the Beckman Research Institute Animal Care and Use Committee. Patient samples (Table S9) were obtained in compliance with the internal review board of the Beckman Research Institute of City of Hope.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	GSE expression profiles of diagnostic samples from gene expression microarray data from three large cohorts of patients with pre-B ALL were studied from GSE5314 (the Eastern Cooperative Oncology Group (ECOG) Clinical Trial E2993, Juric et al., 2007), GSE11877 (the Children's Oncology Group (COG) Clinical Trial P9906, Harvey et al., 2010; Kang et al., 2010), St. Jude Research Hospital pediatric ALL (Ross et al., 2003, http://www.stjuderesearch.org/site/data/ALL3/). Patients had MRD tested by flow cytometry with two combinations (CD20/CD10/CD45 or CD9/CD19/CD34/CD45), and were defined as MRD positive or MRD negative at the end of induction therapy (day 29) using a threshold of 0.01% as previously described (Borowitz, M. J. et al. 2008). Then, RNA was purified from 207 pretreatment diagnostic samples with more than 80% blasts (131 bone marrow, 76 peripheral blood) and subjected to microarrays. Log-rank test was used to assess statistical significance. Patient-outcome data with mantle cell lymphoma were studied (https://llmpp.nih.gov/MCL/). Patient-outcome data for AML were studied from TCGA Acute Myeloid Leukemia Project (http://www.cbioportal.org/study/summary?id=laml_tcga_pub#clinical; Cancer Genome Atlas Research Network, 2013).

Recruitment	We are not aware of any potential self-selection bias or other biases present.
Ethics oversight	Human leukemia samples were sourced ethically and their use was in compliance with the internal review boards of the Beckman Research Institute of City of Hope.

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

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.*	Genome wide mapping of IKZF1 binding (ChIP-Seq) in human patient-derived B-ALL xenograft cells (Schjerven H. et al., 2017, GSE58825); Genome binding/occupancy profiling of activation of Cre in Ikzf1exon5fl/fl stromal adherent pre-B cells (Hu Y. et al., 2016, GSE86897)
Files in database submission	Genome wide mapping of IKZF1 binding (ChIP-Seq) in human patient-derived B-ALL xenograft cells (Schjerven H. et al., 2017, GSE58825); Genome binding/occupancy profiling of activation of Cre in Ikzf1exon5fl/fl stromal adherent pre-B cells (Hu Y. et al., 2016, GSE86897)
Genome browser session (e.g. UCSC)	Genome wide mapping of IKZF1 binding (ChIP-Seq) in human patient-derived B-ALL xenograft cells (Schjerven H. et al., 2017, GSE58825); Genome binding/occupancy profiling of activation of Cre in Ikzf1exon5fl/fl stromal adherent pre-B cells (Hu Y. et al., 2016, GSE86897)

Methodology

Replicates	Genome wide mapping of IKZF1 binding (ChIP-Seq) in human patient-derived B-ALL xenograft cells (Schjerven H. et al., 2017, GSE58825); Genome binding/occupancy profiling of activation of Cre in Ikzf1exon5fl/fl stromal adherent pre-B cells (Hu Y. et al., 2016, GSE86897)
Sequencing depth	N/A
Antibodies	antibodies for RNAPII, H3K4me3 and IKZF1
Peak calling parameters	The ChIP-seq peaks were called by the MACS peak caller by comparing read density in the ChIP experiment relative to the input chromatin control reads, and are shown as bars under each wiggle track.
Data quality	N/A
Software	Integrative Genomics Viewer (IGV) was used to visualize ChIP-seq tracks downloaded from ENCODE.

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	PBS washed cells were blocked with Fc blocker for 10 min on ice and then stained with the appropriate antibodies or isotype control for 25 min on ice. Cells were then washed and resuspended in chilled PBS containing 0.75 µg/ml of DAPI to exclude dead cells.
Instrument	Acquisition was performed by LSRFortessa flow cytometer (BD Biosciences). The fluorescence based cell sorting was performed by FACSAria II (BD Biosciences).
Software	FACS data were analyzed with FlowJo software (FlowJo, LLC).
Cell population abundance	At least 20,000 cells per sample were recorded. Purity was determined by comparison with negative control.

Gating strategy	Single cells determined by FSC-H /FCS-A as well as SSC-H/SSA-A. Then, DAPI negative lymphocytes were discriminated by FCS/ SSC. The Boundaries between “positive” and “negative” were defined by comparison with isotype control.

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