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Reporting Summary

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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	No customized software was used; BD FACSDiva version 6 was used to collect flow cytometric data; Applied Biosystems StepOnePlus real-time PCR system and associated software were used to collect real-time PCR data; Promega GloMax® 96 Luminometer and associated software were used to collect luciferase data; microscope data were collected using Zeiss ZEN and associated software (blue edition). Western blot data were collected by FlourChem E system. Additional information about software was described in the manuscript or available upon request.
Data analysis	No custom-made software was used for data analysis. Statistical analyses were performed using R3.4.0, SAS 9.3, Microsoft Excel 2016 or Graphpad Prism 7. The microscope images were analyzed using Zeiss ZEN software (blue edition). Flow cytometry data were analyzed using Flowjo 7.6 or 10.0. Immunoblot data analysis was performed using AlphaIView software (version 3.2.2.0).

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

All summary or representative data generated and supporting the findings of this study are available within the paper. Raw data that support the findings of this study are available upon request.

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	Most of our experiments are in vitro experiments using donor primary cells. Sample sizes were chosen on the basis of our previous studies or publications, as well as the availability of donors. As a result, assuming a CV of 30%, with 3-9 donors, we were able to detect a group difference of 2-2.5 fold with at least 80% power and type I error controlled at 0.05, after adjusting for multiple comparisons. For simplicity, paired t test or Student's t test was used for the power analysis.
Data exclusions	No data were excluded for all figures.
Replication	All experiments were reliably reproduced and results are represented as mean +/- SEM or +/-SD as appropriate, which is indicated in figure legends. Student's t-tests or paired t-tests were used to compare two independent or two paired groups, respectively. Linear mixed model was used to compare three or more groups with repeated measures from the same donors. A two-way ANOVA model was used to test synergistic effects. P values were adjusted for multiple comparisons using Holm's procedure. A P value of 0.05 or less was considered statistically significant, which is described in the methods section of the main text.
Randomization	Leukopaks used to isolate NK cells were de-identified and randomly picked up. For the experiments with a small sample size, randomization was not used.
Blinding	Considering appropriate handling and data acquisition, investigators were not blinded to the studies. Moreover, because samples were treated equally and data collection and/or analysis were mainly performed by computer-based methods (such as flow cytometric analysis), we believe the blinding was not necessary to our study.

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

Antibodies

Antibodies used	Anti-ACTIN (clone I-19; sc-1616; Santa Cruz Biotech) Applications: Immunoblotting (IF, 1:1000 dilution); Immunofluorescence (1:200 dilution): https://datasheets.scbt.com/sc-1616.pdf

Anti-Lamin B (clone C-20; sc-6216; Santa Cruz Biotech): http://datasheets.scbt.com/sc-6216.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-XBP1 (clone M-186; sc-7160; Santa Cruz Biotech): http://datasheets.scbt.com/sc-7160.pdf
Applications: IF (1:100 dilution)
Anti-T-BET (clone 4B10; sc-21749; Santa Cruz Biotech): http://datasheets.scbt.com/sc-21749.pdf
Applications: IP (immunoprecipitation, 2 µg per 100-500 µg protein samples), IF (1:100 dilution)
Anti-ubiquitinylated proteins antibody (clone FK2; 04-263; Millipore): http://www.merckmillipore.com/CN/zh/product/Anti-Ubiquitinylated-proteins-Antibody-clone-FK2,MM_NF-04-263
Applications: IP (2 µg per 100-500 µg protein sample per sample in our study)
hCD3 (clone SK7; 560176; BD Bioscience): http://www.bdbiosciences.com/ds/pm/tds/560176.pdf
Applications: Flow cytometry (5 ul/test)
hCD56 (clone B159; 557699; BD Bioscience): http://www.bdbiosciences.com/ds/pm/tds/557699.pdf
Applications: Flow cytometry (5 ul/test)
hCD107a (clone H4A3; 560664; BD Bioscience): http://www.bdbiosciences.com/ds/pm/tds/560664.pdf
Applications: Flow cytometry (5 ul/test)
hCD107a (clone H4A3; 561343; BD Bioscience): http://www.bdbiosciences.com/ds/pm/tds/561343.pdf
Applications: Flow cytometry (5 ul/test)
XBP1s (clone Q3-695; 563382; BD Bioscience): http://www.bdbiosciences.com/ds/pm/tds/563382.pdf
Applications: Flow cytometry (5 ul/test)
Mouse IgG1, kappa monoclonal isotype control (ab18443; Abcam): https://www.abcam.com/Mouse-IgG1-kappa-monoclonal-MOPC-21-isotype-control-ab18443.html
Applications: IP (2 µg per 100-500 µg protein sample)
Anti-p-AKT (clone D9E; S473; CST) (4060S): https://media.cellsignal.com/pdf/4060.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-AKT (clone 11E7; 4685S; CST): https://media.cellsignal.com/pdf/4685.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-α-Tubulin (clone DM1A; 3873S; CST): https://media.cellsignal.com/pdf/3873.pdf
Applications: Immunoblotting (1:1000 dilution), IF (1:200 dilution)
Anti-FLAG (clone D6W5B; 14793S; CST): https://media.cellsignal.com/pdf/14793.pdf
Applications: Immunoblotting (1:1000 dilution), IP (1:100 dilution), IF (1:200 dilution)
Anti-STAT5 (no clone information; 9363S; CST): https://media.cellsignal.com/pdf/9363.pdf
Applications: Immunoblotting (1:1000 dilution), ChIP (1:50 dilution)
Anti-GZMB (no clone information; 4275S; CST): https://media.cellsignal.com/pdf/4275.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-Ubiquitin (no clone information; 3933S; CST): https://media.cellsignal.com/pdf/3933.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-T-BET (clone D6N8B; 13232S; CST): https://media.cellsignal.com/pdf/13232.pdf
Applications: IF (1:400 dilution), ChIP (1:50 dilution)
Anti-C-CASP3 (clone Asp175; 9664S; CST): https://media.cellsignal.com/pdf/9664.pdf
Applications: Immunoblotting (1:1000 dilution)
Anti-XBP1s (clone
Poly6195; 619502; BioLegend): https://www.biolegend.com/de-de/products/purified-anti-xbp-1s-antibody-2182
Applications: Immunoblotting (1:1000 dilution), ChIP (1-2 ug per sample)
Anti-HA (clone polyclonal; H6908 Sigma): https://www.sigmaaldrich.com/catalog/product/sigma/h6908?lang=zh&region=CN
Applications: Immunoblotting (1:1000 dilution)
Anti-GAPDH (clone D16H11; 5174S; CST): https://media.cellsignal.com/pdf/5174.pdf
Applications: Immunoblotting (1:1000 dilution)
hGZMB (clone GB11; 560212; BD bioscience): http://www.bdbiosciences.com/ds/pm/tds/560212.pdf
Applications: Flow cytometry (0.2 mg/ml)
hCD56 (clone B159; 560360; BD bioscience): http://www.bdbiosciences.com/ds/pm/tds/560360.pdf
Applications: Flow cytometry (5 ul/test)
Donkey anti-goat IgG-HRP (sc-2020; Santa Cruz Biotech): https://datasheets.scbt.com/sc-2020.pdf
Applications: Immunoblotting (1: 10,000)
Rabbit IgG HRP Linked Whole Ab (NA934-1ML; E Healthcare): https://www.sigmaaldrich.com/catalog/product/sigma/gena9341ml?lang=zh&region=CN
Applications: Immunoblotting (1: 10,000)
Mouse IgG HRP Linked Whole Ab (NA931-1ML; GE Healthcare): https://www.sigmaaldrich.com/catalog/product/sigma/gena9311ml?lang=zh&region=CN
Applications: Immunoblotting (1: 10,000)

Validation

No customized antibodies were used. Validation data about the antibodies purchased from commercial vendors are available on the manufactures' website (see antibodies used for the link of each antibody) and/or datasheets sent to us. We used primary human cells or cell lines that are known to be positive for a specific antigen or target protein for validation of antibodies that were used for flow cytometry and immunoblotting.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

The K562 and NK-92 cell lines were purchased from ATCC. The U937, MM.1S, and MOLM-13 cell lines were obtained from the Caligiuri laboratory.

Authentication

Cell lines were not independently authenticated, beyond the identity provided from the supplier (e.g., ATCC).

Mycoplasma contamination	Stocks of all cell lines were tested for mycoplasma contamination prior to use in this study. All were negative.
Commonly misidentified lines (See ICLAC register)	No cell lines used in this study are in the database of commonly misidentified cell lines.

Human research participants

Policy information about studies involving human research participants

Population characteristics	We purchased leukopaks from the American Red Cross or obtained samples from OSU Comprehensive Leukemia Tissue Banks. All samples are de-identified and no populations were excluded.
Recruitment	Recruitment is not relevant to this study. There are no clinical trials involved, and the majority of samples were purchased from the American Red Cross.

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	Cells were labeled with monoclonal antibodies at room temperature for 15 minutes and washed with PBS containing 2% BSA prior to analysis using an LSRII flow cytometer (BD Biosciences) to detect surface expression of each antigen. The NK cells were gated as CD56-FITC(+)CD3-APC-H7(-) lymphocytes. For CD107a assays, NK cells were co-cultured with tumor cells for 4 h in the presence of GolgiStop (BD), followed by staining with an anti-CD107a-APC or anti-CD107a-APC-H7 antibody. For the intracellular flow cytometric analysis, cells were permeabilized and fixed using a Foxp3/Transcription Factor Fixation/Permeabilization kit (eBioscience), followed by staining with anti-XBP1s-V450 or anti-GZMB-APC antibodies. Data were analyzed using FlowJo v10.
Instrument	Samples were analyzed on an LSRII (BD) or FACSAria II unit (BD)
Software	Data were collected using FACSDiva (BD) and analyzed using FACSDiva (BD) or FlowJo v7.6 or v10. Graphing and statistical analysis were performed using Prism 7 (GraphPad).
Cell population abundance	When applicable, cell populations were sorted to >95% purity in all experiments, as determined by flow cytometry.
Gating strategy	Unless otherwise indicated, positive and negative gates were set using fluorophore-matched IgG controls. NK cells including those co-cultured with tumor cells were gated on CD3 negative and CD56 positive.

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