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Corresponding author(s): Benjamin Gewurz

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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	FACS data were acquired by BD FACSCalibur using Cell Analyzer Software. Western blot data were acquired by Licor Odyssey Fc Imaging System using software Image Studio ver. 4.0.
Data analysis	The statistical significance of CRISPR screen hits was calculated using the STARSs algorithm v1.3. For RNAseq analysis, adaptor-trimmed Illumina reads for each individual library were mapped back to the human GRCh37.83 transcriptome assembly using STAR2.5.2b. DESeq2 was used to evaluate differential expression (DE). Gene ontology analysis was performed with Enrichr on-line tool. The FACS data were further analyzed with FlowJo (version V10). Heatmaps were generated by using a online tool- Morpheus (https://software.broadinstitute.org/morpheus/). All numerical and statistical data analysis were performed by Graphpad Prism 7. Confocal microscopy data analysis was performed by Zeiss Zen2012(Blue edition). The principle component analysis was performed using prcomp() function and visualized with ggplot2 (version 3.2.1) in R-3.5.2.

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

All relevant data supporting the findings of this study are available within the article and its supplementary information files, or from the corresponding author on request. The accession numbers for RNA-seq datasets reported in this paper are GSE136596, GSE136597, and GSE136609.

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	Power calculations were performed for pairwise comparisons of independent groups of quantitative data. Using group size of at least n=3 guarantees the power for a hypothesis test at the 5% significance.
Data exclusions	No data were excluded from the analysis.
Replication	All experiments were biologically repeated multiple times to verify the reproducibility of the results. Those results were consistent between different replicates.
Randomization	N/A. All the experiments were done in vitro.
Blinding	N/A. All the experiments were done in vitro.

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	Anti-LMP1(OT-21C), anti-EBNA1(OT1X), and anti-BMRF1(OT14E2) antibodies were obtained from Dr. Jaap Middeldorp. Anti-EBNA2(PE2) and anti-gp350(72A1) antibodies were obtained from Dr. Elliot Kieff. Anti-EBNA3C antibody(A10) was obtained from Dr. Michelle J. West. Anti-UHRF1 (D6G8E, Cat#12387S), anti-DNMT1(D63A6, Cat#5032S), anti-BCL-6 (D4I2V, Cat#14895S), anti-TRAF1 (45D3, Cat#4715S), anti-RING1A(2820, Cat#2820S), anti-IRF4(Cat#4964S), anti-DNMT3B (Cat#57868S) and anti-H2AK119Ub1 (D27C4, Cat#8240T) antibodies were purchased from Cell Signaling Technology. Anti-LMP2A(15F9, Cat# ab59028) were purchased from Abcam. Anti-SCML2 (F-7, Cat# sc-271097), anti-LMP1-AF647(Cat#SC71023), and anti-BZLF1(BZ1, Cat# sc-53904) antibodies were purchased from Santa Cruz. Anti-V5-tag (V5-10, Cat# V8012-50UG) and anti-Flag-tag(M2, Cat# F1804) were purchased from Sigma-Aldrich. Anti-DDX1(Cat#A300-521A-T) antibody was purchased from Bethyl. Anti-histone H3K9me3 antibody(Cat#39161) was purchased from Active Motif. Anti-UHRF1 (ChIP-grade, Cat#C15410258-100) was purchased from Diagenode. ICAM1-PE(Cat#555511) was purchased from BD Bioscience. CD10-APC (Cat#312210) was purchased from Biolegend.
Validation	Anti-LMP1(OT-21C), anti-EBNA1(OT1X), anti-BMRF1(OT14E2), Anti-EBNA2(PE2),anti-BZLF1 (BZ1) and anti-gp350(72A1) antibodies are well known and widely used in the Epstein Barr virus filed (eg. PMID: 26768848; PMID: 28514666; PMID: 31145756; PMID: 29709016; PMID: 28617871; PMID: 30052684; PMID: 27348612). For antibodies against CRISPR screen hits (UHRF1, DNMT1, RING1, SCML2), we confirmed by western blot that a band at the expected molecular weight decreased in signal intensity upon expression of the guide RNA targeting the gene encoding the protein of interest. Anti-BCL-6 (D4I2V, Cat#14895S), anti-TRAF1 (45D3, Cat#4715S), anti-RING1A(2820, Cat#2820S), and anti-IRF4(Cat#4964S) were well validated for western blot by Cell Signaling Technology.

Anti-histone H3K9me3 antibody(Cat#39161) was validated for ChIP by Active Motif.
Anti-UHRF1 (ChIP-grade, Cat#C15410258-100) was validated for ChIP by Diagenode.
CAM1-PE(Cat#555511) was validated for FACS by BD Bioscience.
CD10-APC (Cat#312210) was for FACS by Biolegend.
Anti-V5-tag (V5-10, Cat# V8012-50UG) and anti-Flag-tag(M2, Cat# F1804) are well-known antibodies recognizing epitope tags.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The BL cell lines MUTU I, MUTU III and KEM I were obtained from Dr. Jeffrey Sample. The BL cell lines P3HR-1 cl16, EBV +Akata, EBV- Akata and Daudi BL, and and EBV+ gastric carcinoma NUGC3 cells were obtained from Elliott Kieff. Rael BL cells were obtained from Lisa Giulino-Roth and Ethel Cesarman. JSC-1, BC-1, BCBL-1, and C666.1 cells were obtained from Bo Zhao. The B-ALL REH cell line was obtained from ATCC. GM12878 and GM11380 LCLs were obtained from the Coriell Institute for Medical Research. MUTU I, Rael and P3HR1 cells were authenticated by the Idexx CellCheck 9 - human STR Profile and Inter-species Contamination Test.
Authentication	STR was used to confirm the identity of the MUTU, RAEL, and KEN I cell lines used in the manuscript.
Mycoplasma contamination	Cells were certified as mycoplasma-free using the MycoAlert kit (Lonza).
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in the study.

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	See page 17 "Flow cytometry analysis" section.
Instrument	BD FACSCalibur; BD FACSAria™ III sorter
Software	BD Cellquest Pro was used for data collection. Flowjo X was used for data analysis.
Cell population abundance	For the CRISPR screen, FACSort was used to identify MUTU I Burkitt lymphoma cells that up-regulated ICAM1 and/or down-regulated CD10 as indicated in Figure 1 and S1. All the sorted cells were used for PCR amplification and next generation sequencing. For all validation studies, 10000 live cells were gated. Contuor plot was used for the screen, and histogram was used for the validation studies.
Gating strategy	Gating strategy was decided use of a known negative control samples (for instance, we used unedited MUTU I cells, which are low for ICAM-1, to set the ICAM-1 gate and then sorted for cells that upregulated ICAM1 abundance above this threshold). The same strategy was used to measure ICAM-1 abundance for screen hit validation and mechanistic studies.

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