Supplementary Methods

Cell Culture. The human T-cell lines MAC2A and CUTLL-1 were a kind gift from Dr. Giorgio Inghirami. The human Breast Implanted Associated (BIA)-ALCL cell lines TLBR-2 was a kind gift of Dr. Alain Epstein. HEK-293T cells was a kind gift of Dr. Ciarrocchi. Cell identity was determined yearly. All cell lines were genotyped and routinely tested for Mycoplasma contamination. Cell lines were cultured in RPMI-1640 medium (Gibco) supplemented with 10% FBS at 37 °C in an atmosphere of 5% CO_2. TLBR-2 cells were supplemented with IL2 (20U/ml). Doxycycline hyclate was purchased from Sigma and dissolved in H_2O.

Plasmids and viral infections. pLKO Tet-On vector expressing shRNA against HELLS was generated by cloning synthetic double-stranded oligonucleotides into the pLKO Tet-On vector (Addgene #21915). Vectors were packaged into lentiviral particles HEK 293T-cell line and used for infection of low passages MAC2A, CUTLL-1, TLBR-2, and HEK 293T cells at a multiplicity of infection. Cells were selected with 0.5 µg/ml (for MAC2A), 0.75 µg/ml (CUTLL-1), or 1 µg/ml (TLBR-2 and HEK 293T) of puromycin for 3 days.

Western blot. Western blot analysis was performed using standard techniques. The primary antibodies were: HELLS (Rabbit mAb#7998, Cell Signaling Technology), RNase H1 (H-4) (sc-376326, Mouse, Santa Cruz Biotechnology), Phospho-Histone H2A.X (Ser139) (Mouse mAb#80312, Cell Signaling Technology), β-Actin (AC-15, Mouse, Sigma-Aldrich), and GAPDH (Rabbit mAb #2118, Cell Signaling Technology). All secondary antibodies (rabbit and mouse) were HRPconjugated (GE Healthcare) and diluted 1:3000.

RNA extraction and quantitative PCR (RT-qPCR). Total RNA was extracted by TRIzol (Thermo Fisher Scientific) according to the manufacturer's instructions. One microgram of total RNA was retrotranscribed using the iScript cDNA kit, (Biorad). The amplified transcript level of each specific gene was normalized on the CHMP2A housekeeping gene. ΔΔCt quantification method was used for RT-qPCR analyses. The list of primers used is provided in **supplementary table 2.**

Immunofluorescence (IF)

For γH2AX and γH2AX/ser2P-RNAPII staining, cells were spotted on glass slides using Cytospin (Thermo Scientific), fixed with 4% paraformaldehyde for 15 min, and permeabilized with 0.1% Triton X-100 buffer (0.5% Triton X-100, 20mM Hepes-KOH pH 7.9, 50mM NaCl, 3mM MgCl2, 300mM Sucrose) for 10 min and washed twice. Dots were blocked in PBS-BSA solution (1mg/ml BSA, 2% FBS, 0.1% Triton X-100, 1mM EDTA) for 30 min at room temperature and incubated with γH2AX primary antibody (sc-517348, Mouse,1:200, Santa Cruz Biotechnology, Inc) for 1 hour at RT. Dots were washed in PBS three times and stained with secondary antibodies for 45 min (Cat # A-11001, Anti-Mouse Alexa Fluor™ 488, 1:1000, Thermo Scientific). Dots were then incubated with Phospho-Rpb1 CTD (Ser2) antibody (E1Z3G, Rabbit mAb #13499, 1:200 Cell Signaling Technology) for 1 hour at RT, washed in PBS three times and stained with secondary antibodies for 45 min (Cat # A-11012 Anti-Rabbit Alexa Fluor™ 594, 1:1000, Thermo Scientific). Nuclei were stained with DAPI.

For R-loops staining, cells were fixed with ice-cold methanol for 10 min at -20°C, permeabilized with acetone for 1 min at -20°C, and washed twice for 5 min with 4x SSC (pH 7). Dots were blocked in 5% BSA/0.1% Tween-20/4x SSC (pH 7) for 1 hr at RT. Dots were incubated with anti-DNA-RNA Hybrid primary antibody (clone S9.6, MABE 1095,1:300, Merck) for 1 hour and

30 min in blocking solution, washed in 4X SSC solution (pH=7, Cat.#15557044, Thermo Scientific) for three times and stained with Alexa Fluor™ 488 secondary antibody for 45 min. For R-loops/ γH2AX staining, dots were then incubated with γH2AX primary antibody (NB100-384, Rabbit, 1:200, NovusBio) for 2 hours in blocking solution, washed in 4X SSC solution (pH=7, Cat.#15557044, Thermo Scientific) for three times and stained with Alexa Fluor™ 594 secondary antibody for 45 min (Cat # A-11012, 1:2000, Thermo Scientific). For R-loops/ Ser2P-RNAPII staining, dots were then incubated with primary antibody Phospho-Rpb1 CTD (Ser2) antibody (E1Z3G, Rabbit mAb #13499, 1:200 Cell Signaling Technology) for 1 hour and 30 min in blocking solution, washed in 4X SSC solution (pH=7, Cat. #15557044, Thermo Scientific) for three times and stained with Alexa Fluor™ 594 secondary antibody for 45 min (Cat # A-11012, 1:2000, Thermo Scientific). Nuclei were stained with DAPI.

For RNASE H control, cells were treated with RNaseH1 (MO297L, New England Biolabs) for 2 hours at 37°, washed twice, and incubated in 3% BSA/0.1% Tween-20/4x SSC blocking solution overnight before R-loops staining. Immunofluorescences were detected with Nikon Eclipse (Ni) microscope using 60X.

Fluorescent Intensity Measurement

The nuclear R-loops signal was quantified in at least 1000 cells using NIH ImageJ software and as previously described(1).

Nuclear γH2AX foci were quantitated by manually counting immunofluorescence images, analyzing 500 cells for each independent experiment (n=3).

Colocalization signal measurement

To measure the colocalization between the fluorescence signal of Phospho-Rpb1 CTD (Ser2) and that of the R-Loops, the ImageJ software was used, analyzing the percentage of colocalization area in relation to the total fluorescence area of the cell, comparing the Control vs Doxyclin treatments conditions. Furthermore, a correlation analysis between the two fluorescence signals was conducted using the ImageJ “Colocalization-Finder” tool and expressing the correlation based on the Pearson Coefficient. In total, 10 fields were considered per biological replicate (approximately 30 nuclei per field). Total replicates = 3.

ATAC-seq

ATAC-seq on CTR and HELLS-KD cells was performed as described by Grandi et al(2). Briefly, pellets from 50,000 TLBR2 CTR/HELLS-KD cells (viability>95%) were resuspended in 50 ul of ATAC-seq Lysis Buffer (10 mM TRIS-HCl pH 7.5, 10 mM NaCl, 10 mM MgCl2, 0,1% NP40, 0.1% Tween-20, 0,01% Digitonin) and incubated 3 min in ice. Lysates were diluted with 1 ml of ATAC-seq Wash Buffer (10 mM TRIS-HCl pH 7.5, 10 mM NaCl, 10 mM MgCl2,0.1% Tween-20) and spun 500g, 10 min, 4°C. Tagmentation was performed with Illumina Tagment DNA (TD) TDE1 Enzyme and Buffer (Illumina) using 2.5 ul/sample of TDE1 TD enzyme (Tn5 Trasposase). The nuclear pellet was resuspended in 50 ul of Transposition Mix (TD buffer, TDE1 TD enzyme, 0.01% digitonin, 0.1% Tween-20 in PBS) and incubated 37°C, 30 min while shaking at 1000 rpm. DNA was purified using DNA Clean and Concentrator-5 KIT (Zymo Research) and eluted in 21 ul of Elution Buffer. PCR for fragmented DNA amplification and barcoding was performed with NEBNext Ultra II Q5 2X Master Mix (New England Biolabs) with sample-specific adapters. Samples were quantified with NEBNext Library Quantification kit (New England Biolabs) and amplified for an additional 7 cycles. Final libraries were purified with

DNA Clean and Concentrator-5 KIT and sequenced on NextSeq500 (Illumina) to generate paired-end 2 × 75 bp reads.

Statistical analysis

Statistical analyses were performed using GraphPad Prism Software (GraphPad). Statistical significance was determined using Student's t-test. Each experiment was replicated multiple times (>2 up to 6). All analyses were performed using R software version 4.1.3.

Supplementary Figure Legends

Supplementary Figure 1. (**A**) Pie chart shows the genomic annotation of HELLS. (**B**) Example of a ChIP-seq IGV browser view of HELLS binding (bam), HELLS peak (bed), the input control and RNA-seq tracks representative of direct (PLXNB2 and RAD23A) and indirect (TMEM30A) HELLS targets. Centromeric region was chosen as positive control of HELLS binding. The *y*-axis represents the normalized tag densities relative to hg19 genomic coordinates. (**C**) Western blots show the level of HELLS in T-cell lymphoma cells before (CTR) and after doxycycline (DOX) treatment (48 hours) to induce the shRNA against HELLS. (**D**) RT-qPCR validation of HELLS peaks in HDGs in TLBR-2 $HELLS^{KD}$ cells after doxycycline treatment (48 hours). Each data represents the mean ± SEM (n = 2). Two-tailed t-test. *$p < 0.05$; **$p < 0.01$. (**E**) Western blots show the level of HELLS in T-cell lymphoma cells before (CTR) and after doxycycline (DOX) treatment (48 hours) to induce the shRNA against HELLS. (**F**) RT-qPCR validation of significantly deregulated HDGs in TLBR-2 and MAC2A $HELLS^{KD}$ cells after doxycycline treatment (48 hours). Each data represents the mean ± SEM (n = 2). Two-tailed t-test. *$p < 0.05$; **$p < 0.01$. (**G**) The plot shows the expression value of HELLS in ALK^{-} ALCL patients compared

to ALK^+ ALCL patients. The comparison was considered significant for $p \leq 0.05$ (*). (**H**) Correlation plots show the expression values for genes from ALK^- ALCL patients compared to ALK^+ ALCL patients. For each gene pair, the expression HELLS is on the x-axis, while HDGs is on the y-axis. For visualization purposes, a linear model was fitted to the data in each comparison, with the blue and red lines representing 95% confidence intervals. This visualization was made using a DGCA wrapper function to the ggplot2 R package.

Supplementary Figure 2. The pie charts show the distribution of HELLS peaks at HDGs (**A**) and the genomic distribution of H3K4me3, H3K9me3, and RNAPII peaks in TLBR-2 $HELLS^{KD}$ (**B**). (**C**) Example of a ChIP-seq IGV browser view of HELLS binding (in CTR condition) and H3K9me3 enrichment in a pericentromeric gene. The *y*-axis represents the normalized tag densities relative to hg19 genomic coordinates. (**D**) Example of a ChIP-seq IGV browser view of HELLS binding (in CTR condition), H3K4me3 profile, RNAPII occupancy and mRNA expression (RNA-seq track) in representative HDGs (RAD23A and CD274) and in a HELLS indirect gene (TMEM30A which is modulated in RNA-seq after HELLS KD without HELLS binding). The *y*-axis represents the normalized tag densities relative to hg19 genomic coordinates. (**E**) The Venn diagrams show ATAC-seq peaks global (left) and local (at HDGs, right) overlaps between CTR and DOX conditions in TLBR-2 cells. (**F**) Violin and box plots of the absolute value of the log2 shrunken fold-change (y-axis), obtained by differential enrichment analysis (TLBR-2 $HELLS^{KD}$ versus control, DESeq2 R package), in HELLS not-target genes (no.targets), 195 HDGs with lack of RNAPII loading (group I) and 272 HDGs with RNAPII stalled (group II), grouped by ChIPseeker (R package) categories (panels). On top, p-values associated with beta coefficients estimated by linear regression model with log2 shrunken fold-change as the response variable, and gene groups as the independent variable. (**G**) ChIP-RT-

qPCR detection of ser5P-RNAPII normalized on total RNAPII levels for HDGs in TLBR-2 cell line. Data are representative of five independent experiments and are shown as the mean ± SEM (technical triplicates). Two-tailed *t*-test. *$p < 0.05$; **$p < 0.01$. ChIP-RT-qPCR detection of total RNAPII (**H**), ser5P-RNAII (**I)** and ser2P-RNAPII (**J**) on control regions TLBR-2 cell line. 3' region of β-actin was used as CTR^+ for Ser2P-RNAPII whereas the first exon of β-actin was used as CTR^+ for Ser5P-RNAII and total RNAPII. A non-coding region of RUNX2 was used as CTR^-. Each data represents the mean ± SEM (*n*=3).

Supplementary Figure 3. (**A**) Representative immunofluorescences showing the absence of R-loops in lymphoma cells in the absence (CTR) or presence (DOX) of doxycycline (48 hours). Cells were stained with S9.6 antibody and DAPI. The white scale bar represents 10 μm. For specific quantification of nuclear S9.6 staining, regions of interest were overlaid on the DAPI signal and selectively quantified to exclude cytoplasmic S9.6 signal and nucleolar S9.6 signal (n = 3 independent experiments). Relative bar plots indicate the intensity of S9.6-stained cells per nucleus (n=1000 cells). Each data represents the mean ± SEM (n= 3). Two-tailed *t*-test *$p < 0.05$; **$p < 0.01$ relative to CTR. (**B**) Qualitative analysis of the colocalization signal. On the left, representative scatter plots retrieved using the Colocalization Finder plugin on Fiji to analyze the intensity correlation between R-loops and ser2P-RNAPII, as described in Materials and Methods. Red (ser2P-RNAPII) and green (R-loops) signals were plotted on the X and the Y axes respectively. The Pearson's Coefficient is indicated in the upper right part of the plot. On the right, quantification analysis of the percentage of colocalization between red (ser2P-RNAPII) and green (R-loops) signals. Statistical analyses were performed with t-test to compare the data with two variables. Statistical significance is specified with asterisks (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). (**C**) Representative DRIP-qPCR signal values at

the RPL13A (positive control) and SNRPN (negative control) loci in TLBR-2 control and HELLS^{KD} cells w/o pretreatment with RNase H. (**D**) Western blot shows the downregulation of HELLS and the up-regulation of yH2AX in HEK-293T HELLS^{KD} cells after treatment with doxycycline (DOX, 48 hours). β-actin was used as a loading control. (**E**) Western blot shows time course expression of RNaseH1 isoforms in HEK-293T cells. β-actin was used as a loading control. (**F**) Western blot shows changes HELLS and yH2AX 293T HELLS^{KD} cells overexpressing RNaseH1 isoforms w/o treatment with doxycycline (DOX, 48 hours). (**G**) Representative IF images of R-loops and γH2AX intensities in HEK293T HELLS^{KD} cells. w/o treatment with doxycycline (DOX, 48 hours). The white scale bar represents 10 μm. (**H**) Representative ChIP-qPCR signal values at the negative control loci in TLBR-2 control and HELLS^{KD} cells.

(**I**) The effects of doxycycline on NHEJ, MMEJ, and HR efficiency were examined in HEK-293T cells using the GFP reporter assay.

Supplementary Figure 4. Graphs showing the relative cells growth of TLBR-2 HELLS^{KD} (**A**), MAC2A HELLS^{KD} (**B**), and CUTLL1 HELLS^{KD} (**C**) cells treated with different concentrations of chemotherapeutic drugs (Gem: gemcitabine, ETP: etoposide, CISP: cisplatin, CPA: cyclophosphamide) for 96 hours. (**D)** Western blot shows the downregulation of HELLS in CUTLL1 HELLS^{KD} cells after treatment with doxycycline (DOX, 48 hours). GAPDH was used as a loading control. (**E**) RT-qPCR validation of HELLS and significantly deregulated HDGs genes in CUTLL1 HELLS^{KD} cells after doxycycline treatment (48 hours). Each data represents the mean ± SEM (n = 3). Two-tailed t-test. $^{**}p < 0.01$. (**F**) The graph shows the growth of CUTLL1 HELLS^{KD} cells after doxycycline treatment (48 hours). Each data represents the mean ± SEM (n = 3). Two-tailed t-test. $^{**}p < 0.01$. (**G**) Representative immunofluorescences showing

the presence of γH2AX in CUTLL1 HELLS^{KD} cells in the absence (CTR) or presence (DOX) of doxycycline (48 hours). Cells were stained with γH2AX antibody and DAPI. The white scale bar represents 10 μm. (**H**) The table shows the percentage of lymphoma cells proliferation reduction after treatment with doxycycline alone (DOX) or in combination with drugs (GEM: gemcitabine, ETP: etoposide, CISP: cisplatin, CPA: cyclophosphamide) at 96 hours.

Supplementary Table 1. List of genes analyzed by nCounter platform

Gene	**Type**
ACTG1	Coding gene
BATF3	Coding gene
BIRC5	Coding gene
CDC42SE2	Coding gene
CDC6	Coding gene
CENPF	Coding gene
CHMP2A	Coding gene/housekeeping
COG7	Coding gene/housekeeping
DNAJC14	Coding gene/housekeeping
DOCK3	Coding gene
ECT2	Coding gene
EIF2B4	Coding gene/housekeeping
EMC7	Coding gene/housekeeping
ERCC3	Coding gene/housekeeping
EXO1	Coding gene
FLNA	Coding gene
FSCN1	Coding gene
G6PD	Coding gene/housekeeping
GUSB	Coding gene/housekeeping
HELLS	Coding gene
HMGA1	Coding gene
HPRT1	Coding gene/housekeeping
KCNMA1	Coding gene
KCNQ1OT1	Coding gene
KDM4C	Coding gene

KLHL21	Coding gene
KMT2C	Coding gene
MCM5	Coding gene
MHY9	Coding gene
MRPS5	Coding gene/housekeeping
MSH6	Coding gene
MTMR14	Coding gene/housekeeping
NCOR2	Coding gene
POLD1	Coding gene
PPIA	Coding gene/housekeeping
PPIF	Coding gene
REEP5	Coding gene/housekeeping
RHOA	Coding gene
RICTOR	Coding gene
SEPTIN5	Coding gene
SF3A3	Coding gene/housekeeping
STAT5A	Coding gene
SUN2	Coding gene
TLK2	Coding gene/housekeeping
TNFRSF8	Coding gene
TRIO	Coding gene
USP22	Coding gene
XRCC6	Coding gene

Supplementary Table 2. List of primers used in this study

Primers ChIP		
	Forward	Reverse
MCM5_1	CACCGCCTCTTGTTTTTCCC	CTCCCACTAGCCTCACCTCT
MCM5_2	CTGTTCTGGCCGTTTGTTCC	CCGAAGCTGTCGCTGTAGAA
MCM5_ 3	TTTCTGTCCCACGAAGGGGA	TTCCCACTCCATGAAACGCC
MCM5_ 4	TGACCTGTCACCTCCATCGT	AAACCGGAGCACTCAAGTCA
EXO1_1	TGTAGGCAAGTTACCCGTGTT	GCCGATTGCGGTTGGAGAAA
EXO1_2	GGTTTCTCCAACCGCAATCG	AAGGGAACCCACCCATTAGC
EXO1_3	CGAGGATATTTGCCTGGCCC	CTCACTCCGAGGAAAACGGA
EXO1_4	AATGCAGACTGCTGCAAAGC	GCCTCATTCCCAAACAGGGA
RHOA_1	CAGGCAACGAATCCGAGTCC	TTCGTCTCCGAGTTTGCGAC

RHOA_2	ACAGCGACTTCGACTAAGCA	TGGGGTCTGTTTTGAGTGGA
RHOA_3	CTCGCAACAGTCCTCCTGTA	TAGCAGTGCGACTGACGTTG
RHOA_4	TCTTCCCACGTCTAGCTTGC	GCAAACAGGATTGGCGCTTT
RHOA_5	CTCTGGGAGGGAACCTGGATA	CACGCCTGAGGCAATTAGACA
ACTB (β-actin)_downstream	GTCCCTTCCCACCTCCTCAA	GGCCCTTCTATGTCTCCCCA
ACTB_exon1	GCAAAGGCGAGGCTCTGT	CCCTATAAAACCCAGCGGCG
RUNX2_upstream	TCTCAAGGTGCCTGTCTGC	TGAAGTTTGGCCTCTGGTCT
MCM5_peak1	TGAGCGTGGAGGTTCTTGTC	CCGAGAAACTCCTGTCCCAC
MCM5_peak2	GTCACACCTGGTGAAGATCCC	TGCGGCACTGGATAGAGATG
CDC42SE2_peak1	AGGAGCTCTTTTAGGGCAGG	CCCAGAATTGCATATCCAGCC
CDC42SE2_peak2	TGAGCAGTGGCTGAGACAAG	ACCAGGCACAGTTCCAAGAA
XRCC6_peak1	CCTTGCTAGAGGGTTAGCGT	GAGCGTGGTCTCGAGTCTG
MSH6_peak1	TCCGGTCTTCCTTCTGTTCC	AGTTATTCAAAGAAGATGCATTGGT
STAT5A_peak1	TTTGGGATTTCCAGAGCCCG	CGGGGCGGGTCAGAATAG
BATF3_peak1	GTGGGTGATGGACCCTTGATT	CGTGGCGCAAGATACACTCA
BATF3_peak2	GGAGGTGATAATAAGCAGGCTCT	ACAAGGCTGAGCAATCATTTTCG
TNFRSF8_peak1	TGGTTTTAACAGCACCAGCG	CAGAACAGACCGATCGGAGA
TNFRSF8_peak2	AAGGAAGTACCAGGCTCCCA	CGATCCACTCACCAGCAAGG
neg_CTR_HELLS	CAGGACCCCACAGTGTGTC	GCGTTTTGAGCCCTCTATGAG
neg_CTR_DSB	ATGTTCCCCAAGCAGTGTTC	CAGAAGGAGCCCAGAGATTTT
Primer qRT-PCR		
	Foward	Reverse
XRCC6	CTTCCCTGCGCCAAAGTGAG	CAGCCCAAGGTTTCCTCATA
HELLS	AGCGGTTGTGAGGAGTTAGC	CATGCCTGGACACTCACCC
YEATS2	GCCACAGTATCCGGACTGTT	GCACCCCTCCAGATGTGTTT
CDC6	AAGCTGTCTCGGGCATTGAA	GCTGAGAGGCAGGGCTTTTA
MCM5	AGAGGCTCCCTGATGGACTT	TCCCAGACGTGTATACCCCA
EXO1	AGCTACGCTGGGCAATATGT	ACTTCTTGAATGGGCAGGCA
HUWE1	AGGCTGAAACCGACTCAGTG	GATCCGCCATCCCTCTCAAG
JAK2	TACCTCTTTGCTCAGTGGCG	AACACTGCCATCCCAAGACA
UPF1	AATTTGGTTAAGAGACATGCGG	TCAGGGACCTTGATGACGTG
POLK	GCACAAAGGAGAAGTGTGACAG	CCCCTTCGTGGCTTCCATTA
ATM	GCGTGGCTAACGGAGAAAAG	TGTGATGTATGCCTCACTGC

KDM4C	ACAGCCTCTGACATGCGATT	AAACCTGGAGCTCAGCACTC
NABP1	AGAACGGGGCAGTTAGTACG	GAACCACTCCGCACACCAA
RFWD3	GGTAACTACCGAGTCTTCGGC	TCGGCATGATTTAACTGCACC
ATRX	TGATTGTACAGCCAGAGCCAG	CCCATCTTCTCCGCGTTTTT
POLD1	AAACGCTGTTTGAAGCGGCA	GAGGTGCATCATCATCATCCCA
MSH6	TGCTTTTAGGAGCTCCGTCC	CTGTACAGGGTGCTCTGTCG
NCOR2	GCCTTACATGCCTCTGGGAA	CTCGGTGTCTGAGCTGTTGT
HMGA1	CTAATTGGGACTCCGAGCCG	GTAGCAAATGCGGATGCCTT
USP22	CATGACCCCTTTCATGGCCT	TTGTTGAGACTGTCCGTGGG
RAD23A	AACTACATCCAGGTGACGCC	CGCGAAATAGGCCTGGATGA
RHOA	GGACTTAAGCGTCTGGCTC	AGTGCCACCCATGAGAACTG
KLHL21	TTTGTCAGGGATGACTCCGC	CATGTACCTGATTCATGGACGG
CDC42SE2	GCGACGATAGGGCCAGATTT	TGCATACAGATGACCGCAGA
STAT5A	GTCACGCAGGACACAGAGAA	AACCAGGCCTCCAGAGACA
CD30 (TNFRSF8)	GCTTGTGGATTCCAGACCCA	GTGGCTGGCTCATTAACCCT
CHMP2A	ATGGACCTATTGTTCGGGCG	TCTCTAGTTTCTGTCGCTCGC
DRIP-qPCR		
	Foward	Reverse
SNRPN	GCCAAATGAGTGAGGATGGT	TCCTCTCTGCCTGACTCCAT
RPL13A	AGGTGCCTTGCTCACAGAGT	GGTTGCATTGCCCTCATTAC

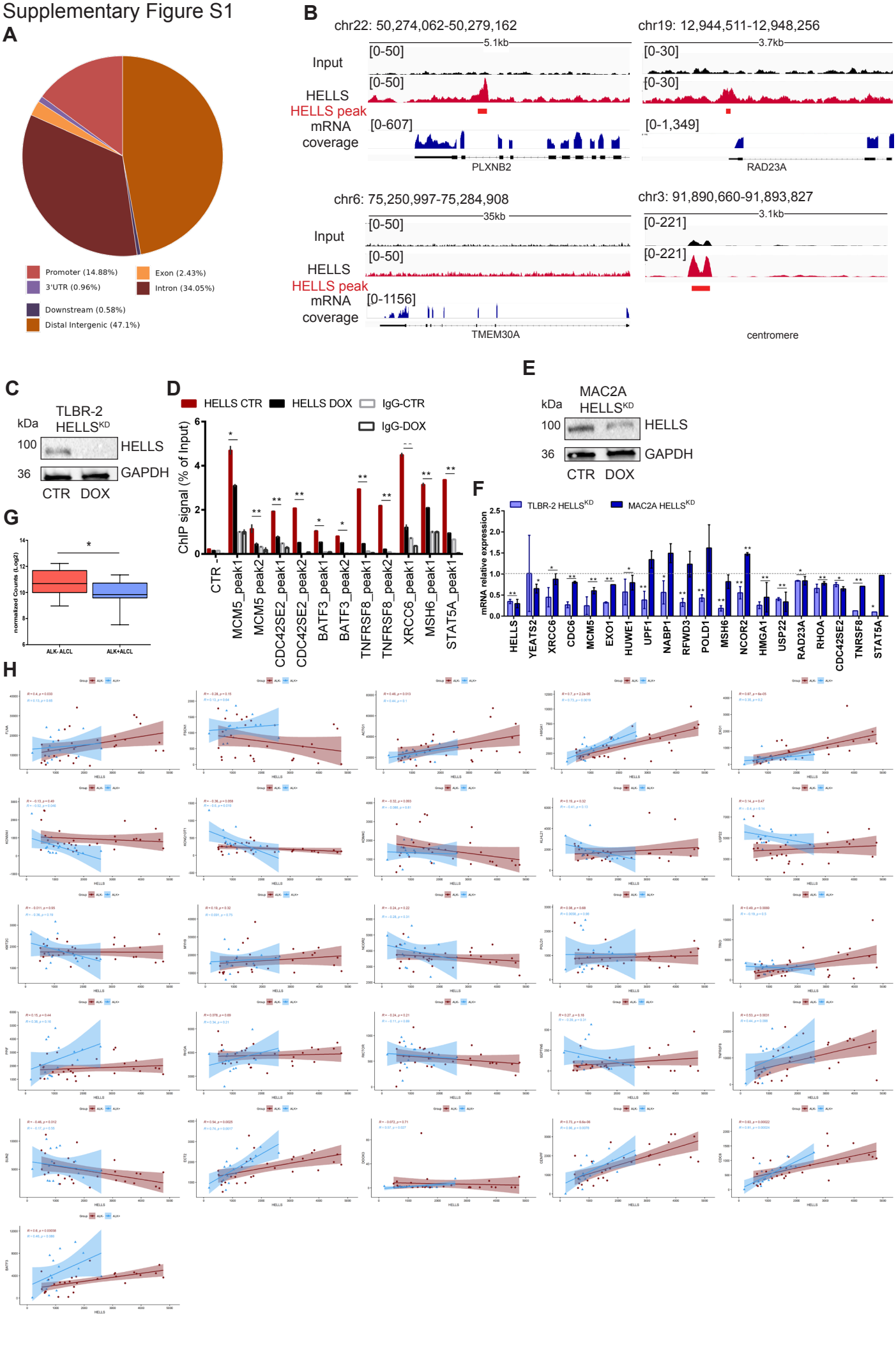
Supplementary Table 3. Number of peaks and corresponding genes for each ChIP-seq condition in TLBR-2 HELLS^{KD} cell line

Sample		# Peaks	# Genes
RNAPII	CTR	76005	15779
	DOXI	80250	16559
H3K4me3	CTR	24080	14140
	DOXI	21377	13484
H3K9me3	CTR	651	84
	DOXI	243	30

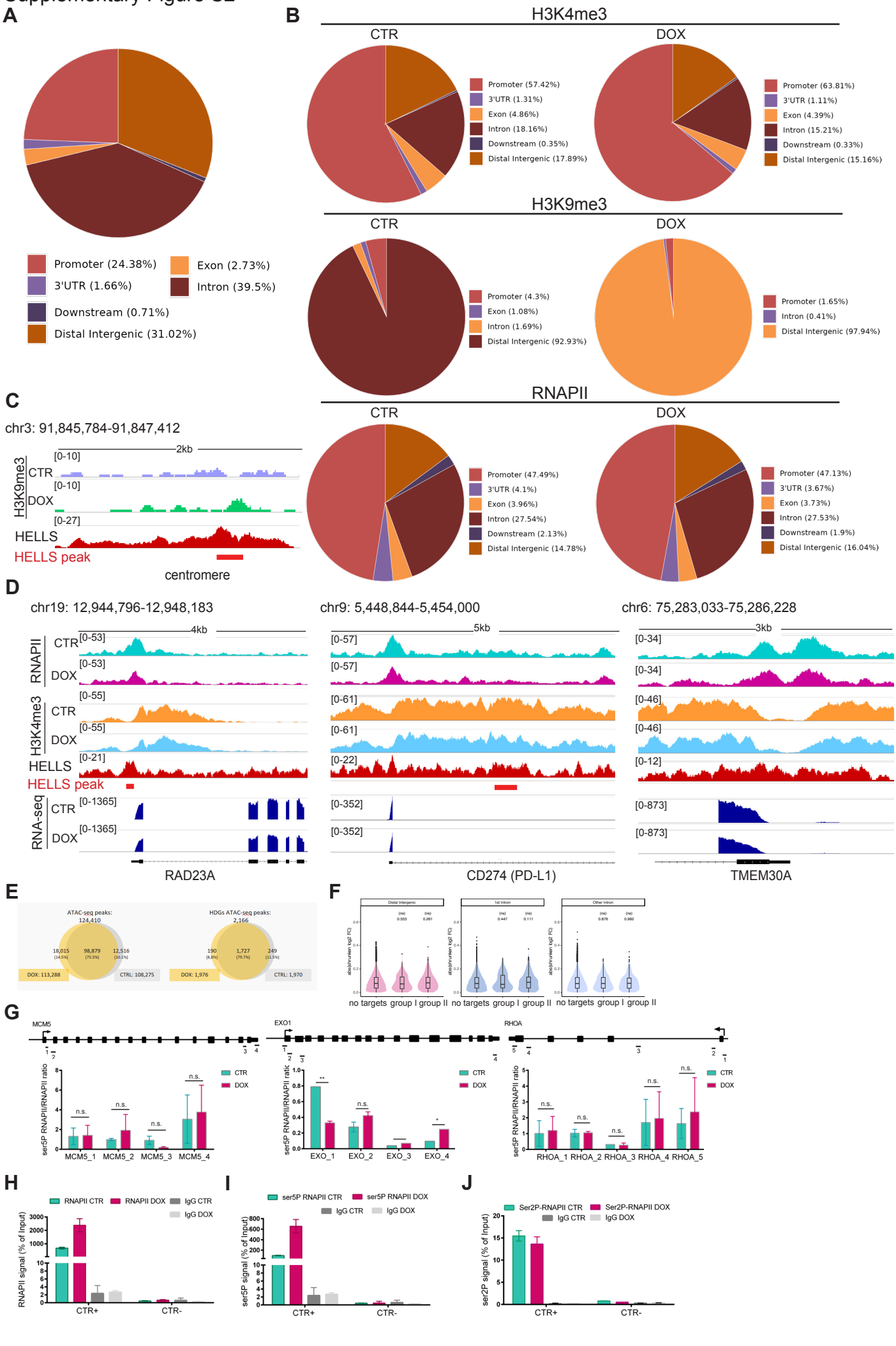
Supplementary References

1. Wahba,L., Amon,J.D., Koshland,D. and Vuica-Ross,M. (2011) RNase H and Multiple RNA Biogenesis Factors Cooperate to Prevent RNA:DNA Hybrids from Generating Genome Instability. *Molecular Cell*, **44**, 978–988.
2. Grandi,F.C., Modi,H., Kampman,L. and Corces,M.R. (2022) Chromatin accessibility profiling by ATAC-seq. *Nat Protoc*, **17**, 1518–1552.

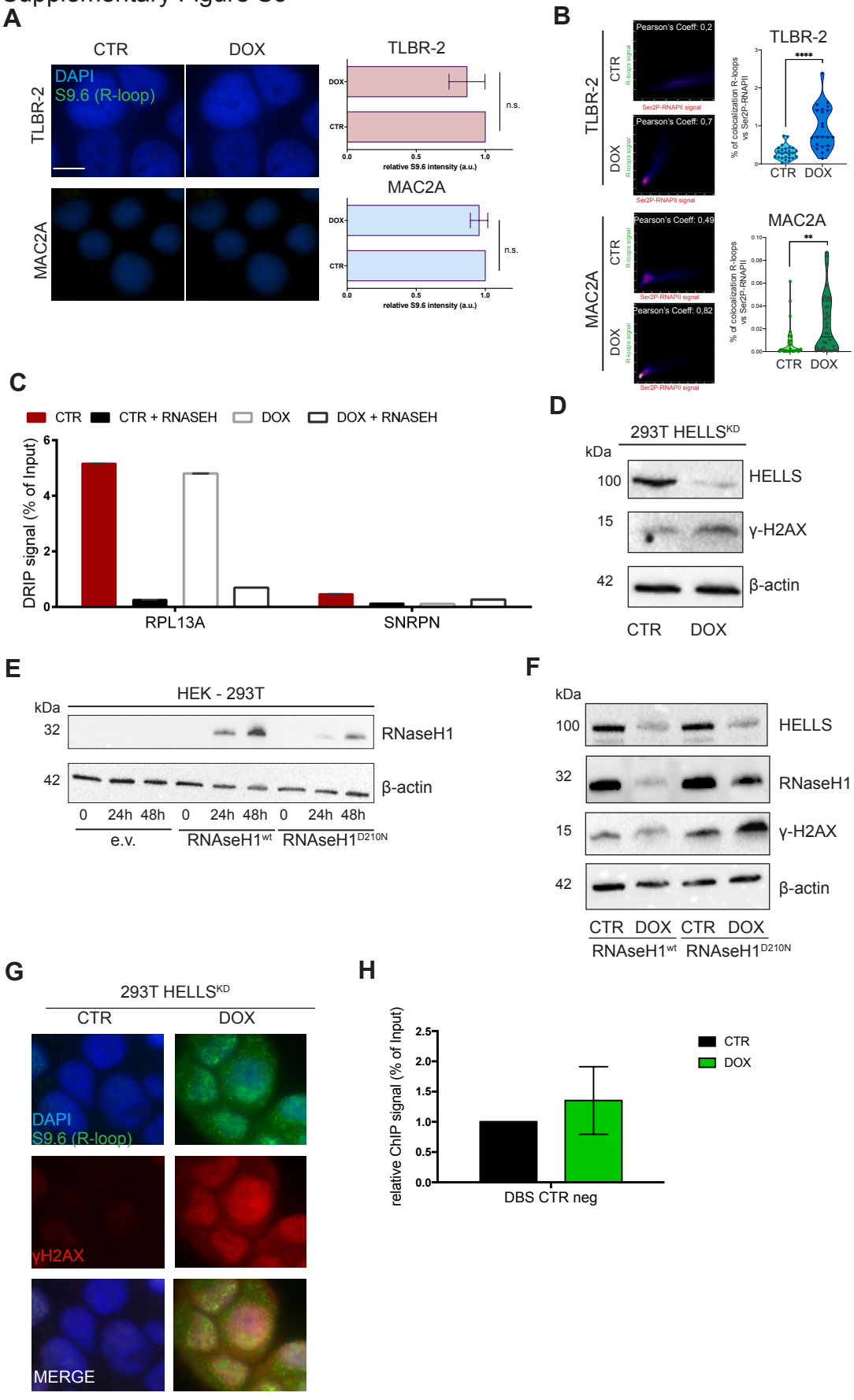
Supplementary Figure S1



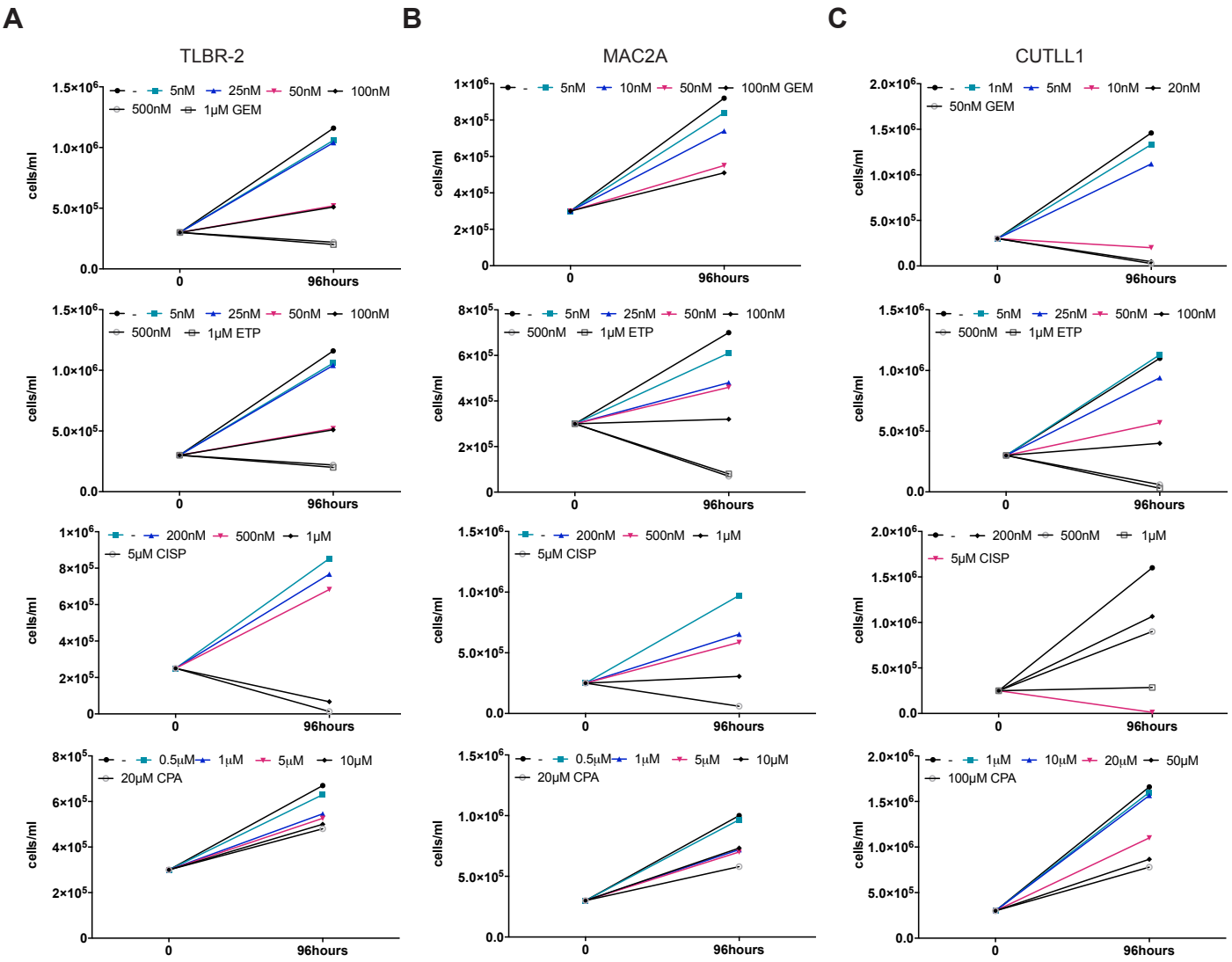
Supplementary Figure S2

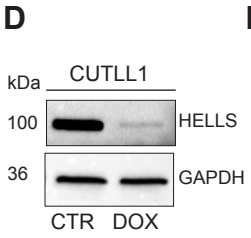


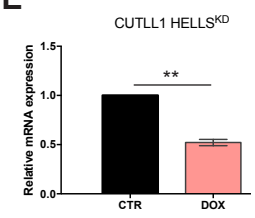
Supplementary Figure S3

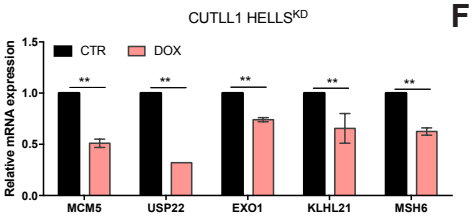


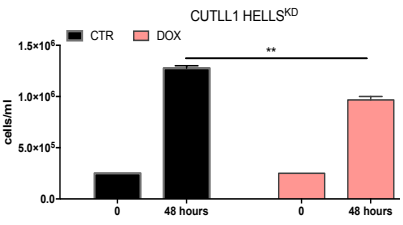
Supplementary Figure S4

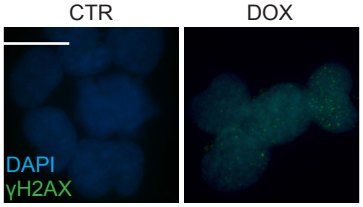












H

	DOX	GEM+DOX	ETP+DOX	CISP+DOX	CPA+DOX
TLBR-2 HELLSKD	22%	39%	40%	36%	30%
MAC2A HELLSKD	15%	35%	29%	23%	20%
CUTLL-1 HELLSKD	14%	35%	28%	11%	28%