

Supplemental Materials and methods

Cloning, virus production, transfection and transduction

For the shRNA sequences and plasmids please refer to the specific section below. All shRNAs were chosen from the TRCN Broad Institute Database based on 100% homology to the target and the lowest off-target prediction (intrinsic score). shRNAs were cloned into Tet-pLKO-puro (kindly provided by Dimitri Wiederschain, Addgene plasmid #21915) and pLKO-GFP (kindly provided by Claudia Scholl, German Cancer Research Center, Heidelberg, Germany) vectors. Cloning was performed according to the Tet-pLKO-puro manual from the Addgene Website - the only modification was the use of Quick[®] Ligase (New England Biolabs) for 5 minutes instead of a normal T4 Ligase. Lentiviral particles were produced by co-transfection with psPAX and pMDG.2 in 293T cells using the Trans-IT LT-1[®] transfection reagent (Mirus). Transduction was carried out one time via spinoculation in the presence of 5 µg/mL Polybrene[®] (Sigma-Aldrich); non-transduced viral particles were removed after 3 hours of incubation. Cells were selected with 1 µg/mL Puromycin (Sigma-Aldrich).

Oligonucleotides

Following qPCR primers were used:

Rad21_forward 5'-AGCAGTGTGGAGAGCATCAT-3'

Rad21_reverse 5'-GGCCGAAACGCCATCTTTAT-3'

Stag2_forward 5'-TGGCTCAAACCGAATGAACG-3'

Stag2_reverse 5'-TCTGCTGTGACGACCTCCTTT-3'

Smc1a_forward 5'-TGCAGTGGAGTCTATTGCCA-3'

Smc1a_reverse 5'-CTCCTTTCGTTTCAGCTGCAA-3'

Etv6_forward 5'-TGGTTCATGCTGTCCTCACG-3'

Etv6_reverse 5'-GAAATTCGTTTCCTGCTGTGTT-3'

Following ChIP-qPCR primers were used:

Klf1_forward 5'-AAGGCTCAGCCCTCGTACTC-3'

Klf1_reverse 5'-AAGTGGCCTTGGTACTGTGG-3'

Cxcr4_forward 5'-TTCAGTCTACCTGCTGCAC-3'

Cxcr4_reverse 5'-ACAGCAGTGGCTCTTGGACT-3'
Epor_forward 5'-GTCCAAAGGACCTAGCACCA-3'
Epor_reverse 5'-TGAGGGAGTCTGGGATATGG-3'

Following short hairpin sequences were used:

shStag2_1 5'-ATTGCGCCAGATCCGAAATAT-3'
shStag2_2 5'- GCGCTTCTTGACCTTATCAAT-3'
shStag2_3 5'- GATAAGAATCTTCTCACATTT-3'
shRad21_1 5'-CGTTGGAGCCCATTGATATAA-3'
shRad21_2 5'- GCACCAGAAATTATGTGACTA-3'
shRad21_3 5'- TCGTTGGAGCCCATTGATAT-3'
shSmc1a_1 5'-GCAGGCATTTGAACAGATAAA-3'
shSmc1a_2 5'-CGACAGATTATCGGACCATTT-3'
shEtv6_1 5'-GCATTAAGCAGGAACGAATTT-3'
shEtv6_2 5'-GCGCCACTACTACAAACTAAA-3'
shLuc1 5'-ATGTTTACTACTCGGATAT-3'
shLuc2 5'-GAATGTTTACTACTCGGAT-3'
shLuc3 5'-ACGCTGAGTACTTCGAAATGT-3'
shScr 5'-CAACAAGATGAAGAGCACCAA-3'

Antibodies

Following antibodies were used:

Rabbit Anti-Rad21 polyclonal Antibody, Abcam Cat# ab992, RRID:AB_2176601
Goat anti-SA2 polyclonal Antibody, Abcam Cat# ab196000, RRID:AB_2716874
Rabbit Anti-SMC1 Polyclonal Antibody, Abcam Cat# ab9262, RRID:AB_307121
Rabbit Anti-CTCF Polyclonal Antibody, Abcam Cat# ab70303, RRID:AB_1209546
Rabbit Anti-H3K27ac Polyclonal Antibody, Abcam Cat# ab4729, RRID:AB_2118291
Rabbit Anti-H3K4me1 Polyclonal Antibody, Abcam Cat# ab8895, RRID: AB_306847
Rabbit Anti-H3K4me3 Polyclonal Antibody, Diagenode Cat# c15410003, RRID:
AB_2616052
Mouse Anti-RNA Polymerase II Monoclonal Antibody, Covance Cat# MMS-126R,
RRID: AB_10013665

Mouse anti_TEL (E-1) Monoclonal Antibody, Santa Cruz Biotechnology Cat# sc-166835, RRID: AB_2101020

Rabbit anti ETV6/Tel Polyclonal Antibody, Abcam Cat# ab185816, RRID: AB_2797417

Mouse anti-beta-Actin Monoclonal Antibody, Sigma-Aldrich Cat# A2228, RRID: AB_476697

Rabbit anti H3 Polyclonal Antibody, Abcam Cat# ab1791, RRID:AB_302613

Rabbit anti H2AX Polyclonal Antibody, Cell Signaling Technology Cat# 2595, RRID: AB_10694556

FITC anti-mouse CD71 Antibody, BioLegend Cat# 113806, RRID:AB_313567

APC anti-mouse TER-119/Erythroid Cells antibody, BioLegend Cat# 116212, RRID:AB_313713

PE anti-mouse CD117 (c-kit) Antibody, BioLegend Cat# 105808, RRID: AB_313217

FITC Anti-mouse/human CD11b Antibody, BioLegend Cat# 101206, RRID: AB_312789

APC anti-mouse CD14 Antibody, BioLegend Cat# 123312, RRID: AB_940575

Briliant Violet 421 anti-mouse Ly-6A/E (Sca-1) Antibody, BioLegend Cat#108128, RRID: AB_2563064

Chromatin fractionation

Chromatin fractionation was performed following the description in¹. Briefly, 50x10⁶ cells were collected by centrifugation (8 min, 300 x g, 4°C) and lysed in 1 ml of buffer A (10 mM HEPES [pH 7.9], 10 mM KCl, 1.5 mM MgCl₂, 0.34 M sucrose, 10% glycerol, freshly supplemented with 1 mM DTT, 1x Complete® (Roche) and 0,1% Triton X-100 (Millipore)) for 5 min on ice. Afterwards, nuclear pellets were collected by low-speed centrifugation (5 min, 1,300 × g, 4°C). The supernatants were further clarified by high-speed centrifugation (10 min, 16,000 x g, 4°C) and saved as cytoplasmic fractions. Nuclear pellets were washed once in buffer A and resuspended in 200 µl of buffer A supplemented with 1 mM CaCl₂ and 0.2 U of Micrococcal nuclease (Sigma-Aldrich). After incubation at 37°C for 1 min, the nuclease activity was stopped by addition of 1 mM EGTA. Nuclei were collected by low-speed centrifugation and lysed in 200 µl of buffer B (3 mM EDTA, 0.2 mM EGTA, freshly supplemented with 1 mM DTT and 1x Complete® (Roche)) for 30 min on ice. Insoluble chromatin fractions were collected by centrifugation (5 min, 1,700 × g, 4°C)

and supernatants were saved as soluble nuclear fractions. Insoluble chromatin was washed once in buffer B and centrifuged again under the same conditions. The resulting pellets containing chromatin were resuspended in 200 μ l 2x Laemmli buffer with 10% of β -mercaptoethanol. Cytoplasmic and nuclear fractions were mixed 1:1 with 4x Laemmli buffer containing 20% of β -mercaptoethanol.

Rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) for analysis of chromatin complexes

Superparamagnetic Dynabeads Epoxy M-270[®] (Thermo Fisher Scientific) were precoated with antibodies over night according to the manufacturer's instruction with 2 differences: 1. Coating was performed at 30°C. 2. After the washing steps, bead-antibody conjugates were incubated in Buffer C (20 mM Tris-HCl pH 7.5, 2 mM MgCl₂, 80 mM NaCl, 1% Triton X-100 and Complete[®] protease inhibitor).

Approximately 100 million cells were suspended in PBS and cross-linked for 8 minutes at room temperature by the addition of 1% formaldehyde, followed by quenching with 125 mM glycine for 5 minutes. Cells were washed 2x in cold PBS, shocked-frozen in liquid nitrogen and stored at -80°C. All RIME preparations were performed with previously frozen cell stocks. Cross-linked cells were thawed on ice, suspended in Lysis buffer A (20 mM Tris-HCl pH 7.5, 0.5% Triton X-100, 2 mM MgCl₂, 1 \times Complete[®] protease inhibitor), incubated for 10 minutes and homogenized with 10 passages through a 19G needle. Clearance was next performed by centrifugation at 16,000 rcf for 10 minutes at 4°C, after which the pellets were further lysed in Buffer B (20 mM Tris-HCl pH 7.5, 2 mM MgCl₂, 200 mM NaCl and Complete[®] protease inhibitor) and incubated for 10 minutes with rotation. After decreasing the NaCl concentration to 80 mM (addition of Buffer B without NaCl), nuclei/chromatins were mechanically sheared by sonication in a Bioruptor Plus[®] sonicator for 10 cycles and 30 seconds with 30 seconds between the cycles. Next, lysates were cleared by centrifugation at 16,000 rcf for 10 minutes at 4°C and incubated with bead-antibody conjugates for 2h. Beads were next washed 1x with Buffer B, 10x with Buffer A and 1x with Urea solution (2M urea (Sigma-Aldrich), 20 mM Tris-HCl pH 7.5). Digestion was performed in 2 steps; step 1 for 30 minutes at 27°C and 800 rpm in Urea buffer plus 5 μ g/ml Trypsin, followed by 2 washes with Urea buffer plus 1 mM DTT and step

2 overnight at room temperature with the pooled supernatants from step1 and washes. Next day, peptides were alkylated for 30 minutes with freshly prepared, light protected Iodoacetamide (IAA, Sigma-Aldrich) solution and acidified with Trifluoroacetic acid (TFA, Sigma-Aldrich). Desalting was next performed in in-house prepared stage-tips with Solution A (0.1% TFA in H₂O) and solution B (50% Acetonitrile (ACN, Sigma-Aldrich), 0.1% TFA in H₂O), while elution was performed prior to the loading into a Thermo Orbitrap QExactive mass spectrometer with Dionex RSLC 3000 UPLC.

Co-Immunoprecipitation

Dynabeads Protein G (Thermo Fisher Scientific, 35 μ l) were incubated with unspecific IgG, antiSA2 and antiRad21 (each with 5 μ g) antibodies for 8 hours in modified RIPA buffer (10 mM Tris-HCl pH 8.0, 1% Triton X-100, 0.1% Na-Deoxycholate, 90 mM NaCl, 1 \times Complete[®] protease inhibitor) prior to cell lysate addition.

To prepare chromatin-enriched lysates, 50x10⁶ cells were collected by centrifugation (8 min, 300 \times g, 4°C) and lysed in 1 ml of buffer A (10 mM HEPES [pH 7.9], 10 mM KCl, 1.5 mM MgCl₂, 0.34 M sucrose, 10% glycerol, freshly supplemented with 1 mM DTT, 1x Complete[®] (Roche) and 0,1% Triton X-100 (Millipore)) for 5 min on ice. Afterwards, nuclear pellets were collected by low-speed centrifugation (5 min, 1,300 \times g, 4°C). Nuclear pellets were washed once in buffer A and resuspended in 200 μ l of buffer A supplemented with 1 mM CaCl₂ and 0.2 U of Micrococcal nuclease (Sigma-Aldrich). After incubation at 37°C for 1 min, the nuclease activity was stopped by addition of 1 mM EGTA. Nuclei were collected by low-speed centrifugation, washed 2x with modified RIPA buffer and finally lysed for 30' with modified RIPA (composition as described above) for 30 min on ice.

Bead-antibody conjugates were then incubated with the nuclear lysates for 4 hours, washed 4x with modified RIPA and finally boiled in 4x Laemmli Buffer freshly supplemented with DTT.

Etv6 was detected with the Mouse anti_TEL (E-1) Monoclonal Antibody, Santa Cruz Biotechnology Cat# sc-166835, which was specifically used to avoid potential confusing 50 KDa bands that frequently occur with rabbit antibodies after Protein G-based pull downs.

RNA-isolation, quantitative Real Time Polymerase Chain Reaction (qRT-PCR) and sequencing

RNA was isolated with the RNeasy Plus Mini[®] Kit (Qiagen) according to the manufacturer's instructions. For RT-qPCR assays, reverse transcription was performed using SuperScript III Reverse Transcriptase[®] (Thermo Fisher Scientific) with oligo-dT primers as per the manufacturer's protocol. Quantitative real-time PCR was performed on a Agilent Mx3000P Instrument using the Brilliant II SYBR[®] Green QPCR Master Mix (Agilent) or on a Thermo QuantStudio 5 Analyser (Thermo Fisher Scientific) using the Luna[®] Universal Probe One-Step RT-qPCR Kit (New England Biolabs).

For RNA-seq experiments, stranded polyA selected libraries were prepared using the TruSeq Stranded mRNA Library Prep Kit[®] from Illumina according to manufacturer's standard protocol. Libraries were subject to 150 bp paired-end sequencing on an Illumina HiSeq 4000 instrument.

RNAseq data analysis

RNAseq reads were quality checked and adapter trimmed using FastQC (S. Andrews, <http://www.bioinformatics.babraham.ac.uk/projects/fastqc>). Reads were aligned to the mouse reference genome (GRCm38 primary assembly, release 82) using STAR two-pass mode (star 2.4.0.1)². Transcript-level counts were generated with HTSeq (version 0.6.1p1)³. Gene annotation was performed with Synergizer⁴. Multiple mappings with the same gene annotation were summed. Normalization, transformation and differential gene expression analysis were performed using DESeq2 version 1.12.4.⁵. Differential expression was considered as significant with a q-value <0.05 and log₂FC>0.5. Gene enrichment was calculated with GSEAPreranked⁶ on all transcripts that were expressed in at least one condition, using "meandiv" as normalization and "weighted" as the scoring scheme. Overrepresentation analysis was performed on defined gene lists with Genomic Regions Enrichment of Annotations Tool (GREAT)⁷ using the standard conditions. Volcano plots were performed in R, Venn diagrams with venny (Stefan Jol - *Make a Venn Diagram*. <https://www.stefanjol.nl/venny>).

ChIP-seq data analysis

ChIP-seq reads were quality checked and adapter trimmed using FastQC. Reads were aligned to the mm10 murine reference genome using Bowtie2⁸. SAM files were converted into BAM format, sorted, de-duplicated and indexed with Picard- (<http://broadinstitute.github.io/picard/>) and Samtools⁹. Reads mapping to repetitive regions or to the mitochondrial genome were discarded. Peaks were called using Macs2¹⁰. Promoter and enhancer regions were defined by the presence of H3K4me3 and H3K4me1, respectively. To avoid multiple comparisons at the same enhancers/promoters, peaks within regions of 5 Kb (for enhancers), respectively 2.5 Kb (for promoters) were merged with Bedtools merge prior to the annotation, which was performed with HOMER¹¹. The genomic region assignment was performed as follows: Rad21 narrow peaks were called with Macs2 independently for both Luc_HPC replicates, accepting model building and lambda. The threshold for significance was accepted at $p < 10^{-5}$. Peaks from both replicates were thereafter intersected and only common events were analyzed in further steps. H3K27ac, H3K4me3, Ctf and Pol2 peaks were also called as narrow peaks, but H3K27ac and H3K4me3 were stitched together if they appeared within regions of < 2.5 Kb using BedTools merge¹². H3K4me1 peaks were called as broad peaks and afterwards stitched together if they were called within regions < 5 Kb, again using BedTools merge. As described earlier, promoters and enhancers were defined as H3K4me3, respectively H3K4me1 positive regions. Additionally, promoters were defined active when positive for H3K27ac and Pol2 and inactive when negative for these marks. Enhancers were considered active when positive for H3K27ac and primed when negative. Insulators/Other elements were mandatory positive for Ctf and negative for all tested marks. All these assignments were performed using BedTools intersect. BigWig tracks were generated from RPM-normalized BedGraphs using the BedGraphToBigWig¹³ script. Differential binding analysis was performed with DiffBind¹⁴ by grouping replicates together. Density heatmaps and avgprofiles were computed with NGSPLOT¹⁵. All other graphs (unless otherwise specified) were performed in GraphPad Prism (version 7.0a for Mac OS X). Browser visualisation of the ChIPSeq signals was performed with the WashU Epigenome Browser¹⁶.

Erythroid differentiation and erythroid perturbation Tier assignment was performed as follows: Signal intensities at each active promoter (H3K4me3 and K3K27ac positive) with ranges of +/-5 Kb were RPM-normalized and outputted on a matrix with replicates of each condition.

Representation of the erythroid differentiation and perturbation tiers, as highlighted in Figures 2B-C and 6A was performed as follows: density heat maps of Rad21 binding sites at active promoters were split into 4 equal tiers based on the increment of the Rad21 peaks during the erythroid differentiation. Shown are examples from one replicate, although the tier assignment was always performed on 2 replicates. To avoid sequencing depth-related bias, peaks binding at active promoters and enhancers were internally calibrated using the ratio to the mean signal at insulators.

Promoter capture HiC analysis

Sample pre-processing was performed with the HiCUP pipeline¹⁷ using the standard settings. The resulting SAM files were converted to the BAM format and processed to the CHiCAGO pipeline¹⁸ with bam2chicago.sh, which only retains the read pairs that mapped, at least at one end, to captured baits. CHiCAGO computation was performed using the standard commands/conditions. CHiCAGO design files were generated using the makeDesignFiles.py script with parameters --minFragLen=150 --maxFragLen=40000 --maxLBrownEst=1500000 --binsize=20000 --removeb2b=True --removeAdjacent=True. Browser visualisation for interactions was performed with the WashU Epigenome Browser. All interactions with at least 5 counts were considered significant. For the data integration with ChIPSeq and RNASeq, computation was performed with normalized hits of significant interactions. Initially, all significant hits per bait end were summed and factorized to the total hit count. ChIPSeq peaks or RNASeq assigned genomic positions were thereafter intersected with the bait end using Bedtools intersect -wb (where b are the pChIC bait ends)¹². For the Figures 5G and S2G a normalization coefficient was calculated as follows: $k = \text{average}(\text{average}(\text{shS2-Ery minus Luc-Ery at gained promoters}) : \text{average}(\text{shS2-Ery minus Luc-Ery at lost promoters}))$.

RIME analysis

Raw data files were analyzed using MaxQuant (1.5.6.0)¹⁹. Parent ion and MS2 spectra were searched against the SwissProt Uniprot Mus musculus protein database released in 2016 using the Andromeda search engine²⁰. Spectra were searched with a mass tolerance of 6 ppm in MS mode, 20 ppm in HCD MS2 mode, strict trypsin specificity and allowing up to 2 miscleavages. Computation of statistics was performed using the Limma package in the R software. The assignment of cis-regulatory-region-binding proteins was performed through gene ontology molecular function enrichment (GO:MF) analysis in STRING²¹ and further confirmed via literature search.

RIME picks up peptides from around 1000 proteins, so that discarding IgG alone as a control might not sufficiently curate the final data. Instead, several curation steps were used to identify chromatin-associated significant cohesin interactors, as follows: i) proteins recognized by less than 2 peptides in less than 2 replicates were discarded; ii) instead of IgG, 4 different shS2_HPC replicates were used as controls for the Stag2 pull-down. The comparison was performed as LFQ intensity in Luc_HPC vs LFQ intensity in shS2_HPC. Most of the pulled proteins were considered false positive, because they were equally strong in both Luc_HPC and shS2_HPC cells. The threshold for significant association was set at $\text{padj} < 0.1$, $\text{log2FC} > 0.33$; iii) RIME-IP was repeated with Rad21 pull-down in 4 Luc_HPC replicates. Again, proteins with less than 2 peptide counts in at least 2 samples were discarded; iv) the final Cohesin interactome was defined as the intersection of the list of proteins from steps ii) and iii).

Sanger MDS and TCGA LAML data analysis

For the Sanger MDS dataset, genes that significantly associated with STAG2 mutations and computation codes were obtained from the previous publication²². Gene enrichment was calculated with GSEAPreranked using “meandiv” as normalization and “weighted” as the scoring scheme.

TCGA_LAML raw HTSeq counts and TPM were obtained from the GDC data portal²³. The differential expression analysis between Cohesin mutated and all other AML samples was performed with DESeq2.

Cohesin/Etv6 gene mutation mutual exclusivity assessment

For assessment of *Stag2* and *Etv6* mutation status from the Cosmic database, curated data was downloaded and further selected for myeloid neoplasia and positive sequencing of both *Stag2* and *Etv6*.

For assessment of Cohesin member gene and *Etv6* mutation status in samples from the UK NCRI AML study group trials, DNA was sequenced using solution-based capture hybridisation and next generation sequencing using a panel of 126 genes and methodology previously described²⁴. Combinations of mutations will be reported elsewhere.

Mutual exclusivity graphs were computed using the CBioPortal OncoPrinter²⁵. Fisher's exact test for mutual exclusivity was confirmed independently.

Supplemental references

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Table S1: Related to Figure 3 - Significant Stag2 interactors

Stag2 interactors	Razor + unique peptides Luc_1	Razor + unique peptides Luc_2	Razor + unique peptides Luc_3	Razor + unique peptides Luc_4	Razor + unique peptides shS2_1	Razor + unique peptides shS2_2	Razor + unique peptides shS2_3	Razor + unique peptides shS2_4	AveExpr	P.Value	padj	log2FC peptides
SMC3	5	7	4	3	1	1	0	0	33076212.5	0.030689825	0.086158242	3.247927513
MCM5	4	4	2	3	0	1	1	0	10349950	0.032068859	0.088513716	2.700439718
VTA1	2	2	1	1	0	0	1	0	8803850	0.004463183	0.033291368	2.584962501
DUS3L	2	2	2	1	0	1	1	0	12306987.5	0.00106692	0.01585598	1.807354922
MED12	2	2	2	1	0	0	1	1	5226662.5	0.02052285	0.072545887	1.807354922
MCM7	1	2	2	2	0	1	1	0	4570360	0.030335836	0.085616258	1.807354922
STAG2	12	14	12	13	4	8	5	2	419058125	0.003415909	0.028394741	1.424497829
MLH1	2	2	2	2	1	1	0	1	8184550	0.000200353	0.007350865	1.415037499
KLF13	2	1	1	1	0	1	0	1	5266587.5	0.011023808	0.050244338	1.321928095
CDC73	2	3	3	2	0	2	2	0	11936075	0.014638737	0.058554947	1.321928095
HIST1H2BF	1	2	1	1	1	1	0	0	5037500	0.028967216	0.084673402	1.321928095
PHF2	2	2	2	1	1	0	1	1	16087262.5	0.016750425	0.064340982	1.222392421
ZC3H14	3	2	3	1	1	0	2	1	4744437.5	0.016326665	0.063708362	1.169925001
RUVBL1	3	3	2	3	2	1	1	1	35599900	0.005162734	0.035439668	1.137503524
CTCF	2	2	2	2	1	1	1	1	59279075	0.000209586	0.00743332	1
RUNX1	2	2	2	2	1	1	1	1	14020012.5	0.001686645	0.020411802	1
WDHD1	2	2	2	2	1	1	1	1	9517686.25	0.001789661	0.020495907	1
TOP2B	4	4	4	4	3	2	2	1	26537312.5	0.002913497	0.02627085	1
NACA	2	2	2	2	1	1	1	1	8271612.5	0.007139876	0.043121155	1
REXO2	2	2	2	2	1	1	1	1	11935712.5	0.012022266	0.053298715	1
FKBP4	2	3	2	1	2	1	0	1	9707375	0.035977073	0.095938861	1
ERG	2	2	1	1	0	1	1	1	6371212.5	0.030813029	0.093147419	1
SMC1A	9	10	9	10	7	4	4	5	141483250	0.002277236	0.023075988	0.925999419
GATAD2A	8	8	6	8	4	3	4	5	55803500	7.27E-05	0.004642967	0.906890596
CRNKL1	3	4	3	3	2	1	2	2	23125200	0.004709434	0.03385701	0.893084796
ADNP	2	3	4	4	1	2	3	1	16535112.5	0.024622597	0.078567258	0.893084796
WAPAL	10	10	11	11	6	7	5	5	195154250	6.53E-06	0.00166624	0.868755467
TCEA1	3	2	2	2	1	1	2	1	31835000	0.001301715	0.017070508	0.847996907
RAD21	7	6	7	7	3	4	4	4	131786625	0.00358717	0.028914763	0.847996907
H2AFV	2	4	1	2	2	1	1	1	22292975	0.021079806	0.072837462	0.847996907
HIST1H2BK	2	2	1	2	1	1	1	1	27193612.5	7.43E-05	0.004642967	0.807354922
PSIP1	2	1	2	2	1	1	1	1	8711050	8.29E-05	0.004642967	0.807354922
PCNP	2	2	2	1	1	1	1	1	6720025	0.001044685	0.01585598	0.807354922
PRPF6	2	2	2	1	1	1	1	1	19206000	0.004280783	0.032328545	0.807354922
DDX39A	1	2	2	2	1	1	1	1	95135750	0.00479865	0.034038422	0.807354922
MARS	2	2	2	1	1	1	1	1	20238750	0.009144569	0.047232144	0.807354922
H2AFY	5	4	4	4	3	2	2	3	28640300	0.000167478	0.006784351	0.765534746
IRF2BP2	5	5	3	4	4	3	2	1	38708712.5	0.003443455	0.028401834	0.765534746
CWC15	1	1	1	2	1	1	0	1	10043687.5	0.01277503	0.054617697	0.736965594
SMARCA4	4	3	2	1	2	1	2	1	13409187.5	0.024949674	0.078857802	0.736965594
RCC2	6	6	5	6	4	4	3	3	62011250	0.007429335	0.043915625	0.716207034

TOP1	3	3	4	3	2	2	1	3	23501637.5	0.000367898	0.009787301	0.700439718
PDS5A	12	12	13	13	7	10	7	7	344154125	2.60E-06	0.001385742	0.689659879
ZC3H4	2	2	2	2	2	1	1	1	14864175	0.000567084	0.011603412	0.678071905
THUMPD1	2	2	2	2	1	1	2	1	26067875	0.001226985	0.017070508	0.678071905
SMAP	2	2	2	2	1	1	1	2	4244961.25	0.00717335	0.043121155	0.678071905
ZC3H18	2	2	2	2	1	1	1	2	9217437.5	0.010656681	0.050201015	0.678071905
TBRG1	2	3	3	3	2	2	1	2	22231675	0.006613115	0.040909035	0.652076697
NARS	3	3	2	3	2	2	2	1	20900050	0.027898332	0.083381533	0.652076697
SMARCE1	3	3	4	4	2	2	2	3	33331600	8.06E-05	0.004642967	0.637429921
RTCB	4	4	3	3	3	2	2	2	26900787.5	0.026787027	0.081265833	0.637429921
EHMT2	2	2	1	1	1	1	1	1	12303196.25	0.000438456	0.010637975	0.584962501
CORO1C	1	2	1	2	1	1	1	1	12561375	0.028880621	0.084652841	0.584962501
TAL1	4	4	4	4	3	3	1	4	64577662.5	0.000961487	0.01550033	0.540568381
PQBP1	4	4	3	2	2	1	3	3	47475100	0.013196955	0.055064942	0.530514717
SSRP1	3	2	2	3	3	1	1	2	12556075	0.010041768	0.049546301	0.514573173
STAT5A	2	3	3	2	2	2	1	2	48829625	0.011007361	0.050244338	0.514573173
ACLY	6	6	6	6	4	4	5	4	160851250	0.015609491	0.061841064	0.497499659
GLYR1	2	1	2	2	2	1	1	1	10532487.5	0.000255393	0.008212543	0.485426827
TSR1	2	2	2	1	1	1	2	1	21833787.5	0.000979937	0.015561983	0.485426827
PSMD5	2	2	2	1	1	2	1	1	65158375	0.001439425	0.018018219	0.485426827
YY1	2	2	2	1	2	1	1	1	8685682.5	0.010313385	0.049653582	0.485426827
RBM17	2	2	2	1	1	1	1	2	18706512.5	0.017551883	0.065527029	0.485426827
GALK1	2	2	2	1	2	1	0	2	13040662.5	0.020214271	0.072417456	0.485426827
ETV6	2	3	3	3	2	2	2	2	68453625	0.000533036	0.011245478	0.459431619
PHF6	3	3	2	3	2	2	2	2	38462375	0.000743397	0.013677449	0.459431619
HMGB1	3	4	4	4	3	4	3	1	31331212.5	0.000367944	0.009787301	0.447458977
MTA2	4	4	5	3	3	3	3	3	56785750	7.93E-05	0.004642967	0.415037499
DPF2	3	3	3	3	2	2	3	2	49768875	0.000169787	0.006784351	0.415037499
THOC1	2	2	2	2	2	2	1	1	32603375	0.001246509	0.017070508	0.415037499
SUPT5H	3	3	3	3	2	1	3	3	14114937.5	0.001305194	0.017070508	0.415037499
DGKZ	2	2	2	2	2	1	1	2	12746162.5	0.002160806	0.02256444	0.415037499
PTMA	3	3	3	3	2	1	3	3	85590125	0.00353413	0.028914763	0.415037499
MCM6	5	5	6	4	5	4	3	3	59008125	0.010117232	0.049546301	0.415037499
RBM7	2	2	2	2	2	1	1	2	17631262.5	0.011107976	0.050244338	0.415037499
HEATR2	2	2	2	2	2	2	0	2	16794500	0.012235661	0.053723155	0.415037499
BOLA2	2	2	2	2	2	2	1	1	10404787.5	0.012527292	0.054136645	0.415037499
NUP107	4	4	4	4	3	4	3	2	44053375	0.020986818	0.072837462	0.415037499
FASN	2	2	2	2	2	1	2	1	22174625	0.029774041	0.084868459	0.415037499
BRD4	3	3	3	3	3	3	2	1	20941012.5	0.019014944	0.06928733	0.415037499
THRAP3	6	7	7	5	5	5	5	4	92331500	0.012566801	0.054136645	0.395928676
PARP1	5	5	6	5	5	4	4	3	55219875	0.001433808	0.018018219	0.392317423
MCM4	6	6	6	4	4	4	4	5	250562500	0.000162215	0.006784351	0.371968777
HIST1H4A	15	15	14	14	14	12	8	11	746117500	0.000485791	0.011161682	0.366127899
MBD3	2	2	3	2	2	2	2	1	8877087.5	0.008441387	0.045443486	0.362570079
ARID1A	2	2	2	3	1	2	2	2	12154550	0.014562613	0.058470266	0.362570079
CAND1	3	2	3	1	2	1	2	2	25561375	0.002783009	0.02530873	0.362570079

LASP1	2	3	2	2	1	2	2	2	20457300	0.0267689 97	0.0812658 33	0.362570079
HMGB2	4	3	4	3	3	3	3	2	54057875	0.0037835 93	0.0298203 19	0.347923303
EIF2A	5	5	5	4	3	3	5	4	88363875	0.0384520 77	0.0998968	0.341036918

Table S2: Related to Figure 3 - All Rad21 interactors

Rad21_interactors	Razor + unique peptides Luc_1	Razor + unique peptides Luc_2	Razor + unique peptides Luc_3	Razor + unique peptides Luc_4	Score	LFQ intensity Luc_1	LFQ intensity Luc_2	LFQ intensity Luc_3	LFQ intensity Luc_4
HIST1H1D	32	32	33	31	323.31	3866500000	4111900000	9103700000	4351800000
HIST1H1A	15	14	13	13	323.31	1070400000	1124400000	2618200000	1155500000
HIST1H1B	17	18	18	17	197.93	1029800000	850690000	2333900000	1019000000
GAPDH	22	23	21	23	206.14	920350000	852430000	682170000	833030000
HIST1H2BF	20	23	21	25	323.31	731800000	909390000	738580000	893610000
HNRNPA2B1	21	24	23	21	323.31	788410000	828620000	876860000	747610000
NCL	38	47	44	52	323.31	632240000	716000000	997460000	671230000
HNRNPA3	7	9	8	9	138.42	612450000	567870000	1066500000	674150000
H3F3A	11	13	12	12	118.8	623950000	701290000	742090000	663400000
HIST1H1E	8	8	8	8	55.45	545770000	467910000	1099900000	551460000
HNRNPU	24	25	25	27	311.61	580700000	592190000	662960000	643020000
VIM	23	26	22	24	267.3	655730000	529780000	616840000	525120000
GM2000	12	12	11	11	151.35	414980000	464460000	699500000	486490000
HNRNPA1	6	7	7	7	122.29	423340000	428260000	621490000	443180000
EEF1A1	19	20	20	21	204.02	385640000	508280000	445120000	505800000
HIST1H1C	11	10	9	11	140.06	309630000	349820000	701020000	334420000
SMC1A	37	42	30	45	301.26	525700000	473060000	218200000	431380000
RAD21	15	17	15	18	187.05	416260000	480720000	175740000	530210000
TUBA1B	8	8	6	10	133.55	351280000	475460000	254220000	505010000
PPIA	14	15	13	15	101.75	337620000	435480000	327030000	405900000
HIST1H4A	11	15	15	14	152.67	306570000	353080000	290840000	386460000
H2AFX	6	6	6	6	25.256	298140000	202780000	457660000	196270000
ACTB	16	14	15	14	162.4	282910000	308550000	208050000	254620000
HIST1H2AF	11	10	10	11	65.847	234370000	268700000	242140000	242020000
PDS5A	22	22	18	24	157.52	259740000	244220000	154310000	229640000
TKT	16	20	18	20	113.39	230440000	231830000	169400000	223410000
NPM1	12	12	13	12	100.4	183720000	202800000	256510000	206250000
HMGA2	5	5	6	5	76.512	183240000	180800000	319880000	159400000
TUBB5	13	13	11	13	84.44	225870000	218920000	116200000	225580000
HNRNPC	15	16	13	16	90.736	166230000	198730000	187750000	214320000
HNRNPK	17	17	14	18	110.08	196260000	195460000	171650000	196550000
PDS5B	20	21	15	23	135.64	196650000	203000000	118900000	206440000
ALYREF	10	9	10	10	319.69	132370000	141560000	280400000	166000000
CBX3	4	5	4	5	80.194	193210000	167650000	195850000	154390000
SERBP1	11	11	9	11	144.65	197750000	159980000	169660000	149640000
LMNB1	10	9	11	10	79.301	132900000	135220000	263660000	133530000
PKM	19	19	19	21	158.77	142670000	165140000	126940000	206930000
SMC3	28	29	22	27	210.18	179270000	203050000	825070000	167370000
KHSRP	16	18	16	18	168.8	144560000	131690000	118360000	154250000
EIF4A3	5	7	5	6	59.995	119560000	127000000	172480000	118550000
G3BP1	12	15	10	14	73.394	143490000	133580000	889860000	141580000

HNRNPA0	8	9	7	8	49.785	120980000	123940000	142450000	119280000
TRIM28	11	13	7	11	150.07	129740000	108700000	102490000	113120000
GM10282	5	5	5	5	68.492	92123000	79963000	175970000	77470000
HNRNPF	10	9	9	10	52.497	86822000	104930000	111510000	113770000
TAGLN2	5	5	5	5	35.267	117640000	91530000	101490000	91792000
HSP90AB1	19	20	19	21	165.5	98628000	111130000	68822000	114840000
SRRM2	15	14	15	15	151.79	88589000	68161000	109260000	77299000
DDX39B	6	10	7	9	75.026	87127000	80340000	92653000	76480000
HSPA8	16	18	18	22	95.796	79122000	86904000	53397000	87996000
EEF2	11	12	11	10	43.514	79420000	83949000	54530000	88377000
NPM3	2	3	2	3	134.86	100820000	56400000	42552000	92378000
PA2G4	10	11	9	10	63.744	78779000	71929000	78499000	61598000
YBX1	8	8	7	8	78.406	92559000	72394000	58653000	65280000
DDX21	12	16	17	15	113.44	70664000	53940000	98856000	64708000
HNRNPAB	11	10	9	10	61.549	72556000	71324000	50958000	77137000
MCM3	10	11	8	11	90.095	75432000	76942000	42488000	75822000
MCM2	6	9	6	8	46.459	63008000	46204000	106410000	54544000
ANP32B	6	8	8	8	39.458	84088000	59388000	60360000	61549000
PARP1	14	12	11	16	82.252	71414000	72332000	51789000	69661000
STMN1	6	6	5	5	83.719	64274000	61827000	69583000	66962000
MCM4	9	7	6	11	51.811	69096000	66749000	56084000	69816000
NONO	10	10	9	11	67.147	59028000	59632000	83883000	57170000
GM6563	8	7	8	7	34.032	64884000	57098000	78336000	57352000
SRSF5	8	7	9	7	34.442	46471000	64222000	79767000	64303000
STAG2	12	13	13	13	99.536	83807000	71604000	25401000	73106000
TPM3	4	3	4	4	44.505	78822000	57077000	53515000	62768000
ENO1	9	8	10	11	49.549	48402000	60370000	67909000	74068000
H2AFY	7	9	6	8	78.352	54172000	50744000	84755000	50136000
WAPAL	10	9	7	10	75.009	68135000	66027000	37747000	63625000
AHCY	6	6	4	6	41.001	60440000	53064000	51406000	66905000
RAN	7	7	6	7	26.881	48900000	53510000	56101000	65470000
CHTOP	6	7	8	7	61.206	49225000	43632000	85741000	41040000
HINT1	3	4	3	3	41.501	66786000	45830000	61282000	45403000
GNB2L1	8	8	7	9	46.418	62774000	58814000	36050000	51277000
CAPRN1	6	6	6	6	21.129	56151000	58660000	37074000	56773000
MCM6	8	7	6	8	44.67	51852000	57673000	42572000	56344000
LGALS9	5	6	4	6	89.933	65498000	55500000	31128000	48820000
UHRF1	9	9	7	9	72.417	47312000	49738000	42969000	59932000
SFPQ	11	10	11	11	45.723	45348000	55157000	43464000	52543000
ALDOA	7	7	4	7	61.958	58353000	49288000	34290000	53447000
PGK1	6	9	8	8	45.738	45509000	51684000	38729000	57644000
FBL	5	7	5	7	23.635	39439000	40764000	62235000	39106000
EIF4H	4	4	5	5	120.94	45942000	40439000	45966000	45292000
PAICS	5	4	3	4	34.901	56606000	38501000	40630000	40930000
HMGA1	6	5	6	7	60.136	38634000	31849000	75309000	29668000
RCC2	7	7	7	8	37.234	34888000	44920000	37839000	54075000

SRSF6	5	7	7	7	40.1	50027000	39171000	51634000	30874000
CPSF6	6	6	4	6	116.06	49948000	41053000	36696000	42003000
HMGB1	7	7	7	7	17.271	43542000	42133000	34233000	46544000
PABPN1	5	5	5	4	83.257	43965000	33038000	53320000	35333000
PHGDH	8	9	7	8	39.261	42038000	41115000	29111000	41488000
DDX17	4	5	5	4	110.15	35433000	37926000	32481000	46105000
SNW1	8	7	7	7	60.527	43342000	37357000	37821000	32491000
CCT4	5	5	6	6	16.675	40423000	39889000	36468000	33777000
TRA2B	3	5	5	4	16.622	32807000	24355000	59255000	25968000
NIFK	3	4	5	4	52.266	31395000	24597000	52926000	30010000
HNRNPL	8	10	9	8	37.849	36646000	40337000	26527000	31774000
LUC7L2	6	5	4	5	19.9	30173000	31638000	34553000	35150000
SSB	6	5	5	5	21.932	22681000	36034000	35662000	36961000
PRPF19	5	6	5	6	64.497	36016000	36011000	19877000	31367000
DDX3X	7	6	7	6	76.695	35201000	28041000	28063000	30029000
SP16H	5	6	3	5	30.483	28336000	28349000	36195000	27280000
CHD4	6	6	5	5	18.44	33801000	26062000	35657000	23799000
CLIC1	5	7	5	7	34.582	36717000	24597000	19300000	38665000
TARDBP	4	4	4	4	65.303	34037000	30318000	23066000	27344000
EIF1AX	4	4	4	4	29.958	20380000	28334000	26871000	38322000
MATR3	4	3	2	3	50.922	28468000	26413000	30750000	27623000
MYBBP1A	7	6	7	6	40.459	20696000	21721000	48376000	21003000
STAG1	8	10	4	9	40.7	32647000	30123000	13874000	31998000
CTCF	5	5	5	4	31.882	34488000	33182000	14583000	26384000
ANP32A	2	4	2	3	28.269	23735000	26474000	24771000	33093000
VARS	5	5	5	6	43.192	27958000	25806000	21855000	30639000
ARPC4	3	3	2	3	19.376	21645000	24406000	26404000	33641000
HMGB2	6	6	6	6	19.615	35856000	25453000	20809000	20562000
PCBP1	5	5	3	5	27.62	37233000	21966000	16190000	25564000
SMARCC1	5	4	2	4	53.604	28732000	23444000	23147000	23842000
PHB	4	3	3	5	19.933	27701000	19699000	24433000	24787000
MCM7	6	7	6	7	31.263	25453000	25387000	21467000	24261000
CCT2	5	3	4	5	79.977	24898000	23824000	14583000	32776000
TOP1	7	6	7	7	24.851	24910000	20512000	22553000	26890000
IGF2BP3	9	9	8	8	39.225	28300000	26667000	19365000	20093000
HP1BP3	8	8	9	7	33.907	23117000	18215000	27492000	24196000
SART3	2	3	2	3	23.934	25300000	18151000	30858000	18267000
TUBB4B	3	3	3	2	16.152	31188000	24112000	13652000	21785000
HDAC1	3	3	2	4	4.9755	22154000	26334000	16959000	24157000
PABPC1	8	7	5	6	28.926	25841000	29443000	14431000	19430000
EIF5A	2	5	3	4	24.062	24745000	24950000	17896000	21129000
RBMXL1	5	6	6	6	23.692	22683000	18208000	25451000	20344000
SRRT	4	4	3	4	8.7794	19723000	20200000	26305000	20339000
DPYSL2	7	7	5	6	20.193	24642000	19930000	21279000	19217000
HDLBP	4	3	2	3	109.04	21572000	17287000	22925000	22144000
XRN2	4	5	4	5	47.518	22004000	18860000	21434000	19113000

H1F0	5	6	5	5	30.311	14613000	10981000	33782000	21642000
SNRPA1	2	2	2	2	28.135	21045000	14437000	28545000	16179000
EIF4A1	4	6	6	4	31.81	26530000	18528000	14388000	20368000
IKZF1	6	6	4	5	38.259	18308000	22579000	15223000	23700000
MYH9	5	5	5	6	44.513	26213000	19000000	14019000	19170000
MTDH	1	2	1	2	15.101	15606000	15382000	31377000	15596000
SND1	7	7	8	7	35.682	20407000	19818000	16162000	19965000
ILF3	3	2	2	2	9.7258	20738000	17041000	24985000	12978000
RFC5	2	2	2	2	12.071	16936000	14732000	29405000	14655000
PDCD11	4	4	5	4	25.014	15691000	10834000	34161000	15022000
ACLY	4	4	4	4	17.506	21408000	19457000	13448000	20142000
VCP	2	1	2	3	70.19	20892000	16110000	17334000	19807000
RBM14	5	6	4	4	21.968	22305000	17339000	18204000	15559000
SNRPA	3	3	4	3	33.968	24781000	15301000	14571000	17737000
POLDIP3	5	7	6	6	45.336	14205000	12538000	29067000	16133000
TMPO	7	9	9	8	62.865	18737000	15414000	19120000	17894000
PFKL	1	2	2	2	29.569	0	23036000	24790000	23076000
TPI1	4	3	2	3	23.969	18695000	17953000	17061000	15483000
COTL1	3	3	3	3	9.695	20698000	15550000	15922000	15296000
CDV3	3	4	3	5	41.003	17941000	17193000	19474000	12634000
GTF2I	4	3	2	3	7.1233	22447000	17780000	13764000	12716000
TOP2B	5	6	6	5	19.272	15097000	15678000	18584000	16686000
NUDT21	3	3	2	2	16.541	17458000	20486000	13712000	13849000
ANXA1	3	3	3	3	89.421	18407000	15091000	13296000	18536000
MSN	7	7	6	8	29.616	16573000	19969000	11692000	16345000
HNRNP1	6	8	6	8	47.683	18248000	13759000	14705000	17561000
LIMD2	2	3	2	3	63.371	18683000	14986000	15087000	14582000
TOP2A	6	5	4	6	31.848	9441000	14258000	23388000	15806000
MTA2	4	6	4	4	45.859	14663000	14565000	17093000	15690000
MCM5	9	7	6	6	24.037	16867000	20041000	9641600	14860000
RUVBL2	4	4	4	4	45.731	21112000	15097000	10675000	14421000
KHDRBS1	3	5	5	5	11.146	14584000	14518000	22466000	9647000
DDX18	4	5	4	5	21.8	15658000	10413000	23567000	10765000
MPO	5	7	5	6	18.845	17847000	14718000	10315000	17398000
SF1	5	7	3	6	18.107	17965000	14201000	12085000	15911000
HSPA9	4	4	4	4	11.233	17324000	15149000	11539000	16133000
PRDX1	4	5	3	5	21.447	14545000	16918000	11806000	15714000
FMR1	4	4	4	3	27.553	16125000	15201000	10729000	16913000
NOP56	2	3	4	3	27.134	12515000	12304000	18985000	14151000
ACTG1	2	2	2	2	34.633	14713000	14623000	12927000	15144000
SRSF3	3	3	2	2	19.005	10642000	14185000	20021000	12410000
QK	4	5	4	5	14.56	14048000	12583000	16326000	13677000
ETV6	2	4	2	3	40.249	15140000	14432000	14246000	11662000
PHF6	2	3	3	3	24.133	10337000	10411000	21618000	12729000
EIF4B	3	3	3	4	12.113	13077000	10286000	18697000	12689000
KDM2A	2	3	3	3	5.4058	0	53515000	0	0

NOP58	4	5	3	4	20.842	10717000	10123000	20017000	12145000
ELF1	3	2	3	3	8.8864	12710000	10780000	17210000	11191000
UBAP2	5	5	5	5	14.514	14301000	13047000	12992000	11224000
CORO7	5	6	5	6	20.059	15383000	12767000	13237000	10141000
TLN1	3	4	3	4	10.471	13634000	12808000	11582000	13113000
GATAD2A	7	8	7	7	26.321	15964000	11144000	11895000	12067000
CSTF2	3	3	3	3	22.513	11566000	10489000	16035000	12952000
BTF3	4	4	4	5	12.057	14181000	13618000	12363000	10360000
U2AF2	2	3	2	2	21.86	13017000	10542000	15303000	11650000
UBA1	3	4	4	3	39.757	13270000	14550000	8497000	13717000
DOCK11	6	5	5	9	24.43	15435000	12956000	8774400	12740000
PHB2	4	6	3	5	18.562	14208000	11975000	9622700	13757000
PRPF8	2	2	2	2	13.682	17053000	11139000	11111000	10212000
GTPBP4	6	4	7	6	23.211	7645300	8598900	23989000	9122200
CDC5L	4	5	4	5	15.305	12265000	11457000	11812000	12973000
RUVBL1	4	4	4	4	7.985	12007000	12122000	9919400	14184000
CASP3	1	2	2	2	15.213	0	15236000	18509000	14457000
HNRNPA3	1	2	2	2	4.6612	0	18646000	20371000	8606400
HSPD1	2	2	3	3	36.151	0	0	13540000	33430000
ADSS	2	3	3	3	24.832	14176000	10782000	9585600	11831000
CCT8	4	5	2	4	15.394	14695000	13249000	7812600	9773700
CSRP1	2	1	2	2	16.887	11172000	0	13488000	20637000
WBP11	3	3	3	3	8.5752	12576000	9731800	14796000	7997500
GM9833	3	3	5	4	10.487	10292000	9715900	13935000	10749000
THRAP3	4	4	4	5	17.391	9792300	9686800	11234000	13656000
PHF2	3	2	3	3	15.687	13093000	10400000	8138700	12175000
AKR1B3	2	2	2	2	12.502	11304000	10714000	10018000	11445000
YTHDC1	3	3	3	3	28.389	7818400	8297700	16990000	10178000
TRMT112	2	2	2	2	6.2332	13129000	9186900	11388000	9012600
LDHA	1	2	2	2	17.349	9699700	14441000	8180200	10292000
LYAR	4	5	5	5	13.258	7857000	7232900	17280000	9748000
LBR	4	2	3	3	11.694	6807800	10896000	13470000	10690000
GCLM	2	2	2	2	11.299	12530000	9408900	9986400	9413900
TCP1	7	8	4	6	29.082	13128000	9945300	7490200	10335000
LGALS1	2	2	2	2	12.43	10378000	13773000	7349300	9261700
POLA2	2	4	3	4	6.9603	12225000	9227100	9979500	9035100
PRPF40A	2	2	3	2	8.4378	12081000	7301400	12536000	7859500
FAM120A	4	3	3	3	12.77	13333000	9644900	6471400	10223000
DPF2	2	2	3	4	10.45	17715000	11498000	0	10222000
CLTC	3	3	1	2	28.066	16785000	12361000	0	10166000
RPF2	2	2	3	2	26.333	5038200	5214000	19927000	8799700
PES1	4	4	4	4	25.292	5868400	6875700	14025000	11613000
BUB3	2	2	2	2	6.321	13992000	13534000	10748000	0
EIF3C	4	4	4	4	12.846	9010600	9879300	9382400	9603700
BCLAF1	4	4	3	3	10.878	14658000	7109900	8395600	7381600
SRM	3	3	2	3	11.044	7122700	8625600	6637900	15139000

SRSF4	3	3	3	3	8.6404	11158000	6892400	11421000	7830600
THUMPD1	2	2	2	2	19.972	10992000	7960700	9256200	8837200
ATP5J2	2	3	3	3	12.172	0	12231000	12033000	12747000
PSMA1	1	2	2	2	16.89	0	12627000	12800000	11399000
PRDX6	2	1	3	2	35.777	10039000	6848200	9143700	10232000
SS18	2	2	2	2	10.806	8939600	7131200	12735000	7162900
PSIP1	3	3	3	3	16.593	11151000	11827000	12352000	0
HCFC1	1	2	2	2	40.817	0	11987000	11849000	11394000
GATAD2B	3	3	2	3	6.7527	9815100	8477000	8569900	8203100
UPF1	5	5	4	4	10.649	10094000	8772600	7366500	8646300
SP110	2	3	4	2	14.092	8232400	7500100	9921000	7982200
FIP1L1	3	3	1	4	21.926	13749000	10507000	0	9315900
ODBA	2	2	2	3	10.569	8644100	10539000	5530900	8204100
BAZ1B	4	4	4	4	16.316	8350800	7395100	9175600	7953900
CACYBP	3	4	3	4	8.8423	10849000	11485000	0	9917800
TAL1	2	2	2	1	8.0419	10105000	10225000	11780000	0
HN1L	2	2	2	2	19.804	7000000	6895600	10658000	6874700
HNRNPUL1	3	4	3	4	14.683	6917000	7283200	6721600	10393000
PQBP1	2	2	2	1	4.9869	8775200	11064000	11383000	0
TUBA4A	2	2	2	2	20.158	7792200	9530600	5298900	8161400
SON	3	3	3	3	16.488	9006300	6635800	8548900	5672300
UTP14A	3	2	6	6	25.306	4544900	4227700	14552000	6438700
ARHGEF2	2	2	2	3	8.127	10887000	8366000	0	10276000
MTHFD1	2	2	2	2	9.323	7106900	7999200	5789300	8609200
STAT5A	2	3	3	3	5.8129	5508300	7898000	7734100	7821900
SRSF1	2	2	2	2	9.133	8704800	7547000	6362900	6301700
PPM1G	2	2	2	2	5.7456	7097800	7812300	6661000	7141000
ZFP706	3	3	3	3	7.7807	7127800	7523400	7962400	6089500
CAND1	2	2	2	2	30.403	8730000	11873000	0	7771700
APEX1	4	4	5	5	11.204	7060500	7761300	5215800	8322300
CDC73	3	3	3	4	8.8439	7283000	6183100	5273100	8959300
ATP5B	2	2	2	2	11.45	10893000	5572900	4315300	6882900
GRB2	2	2	2	2	7.6483	7187200	7454900	6563500	6359400
EMAL4	2	2	2	2	7.9808	8239300	6271300	6867300	6056800
RALY	4	3	3	3	7.1304	12353000	0	0	13626000
BTF3L4	1	2	2	1	8.1846	0	8713800	17056000	0
MSH6	4	5	4	4	11.664	5830200	6126800	4633300	9051200
TCOF1	2	1	3	4	10.486	8259100	0	9828300	7398700
IK	3	3	2	3	18.36	6176500	5734600	6207600	7344000
H2AFV	2	2	2	2	7.3886	0	12677000	0	12613000
GMFG	4	3	4	4	15.115	6343600	7293200	4513700	6687100
ADRM1	1	2	2	2	18.865	0	6961900	10943000	6845200
ACTR2	3	2	2	2	12.767	7814100	6647100	0	10148000
FTSJ3	3	4	4	4	20.52	7303200	5844900	5605400	5379800
DHX15	3	2	2	2	9.5666	6888600	9065300	0	8113100
CAZA1	3	3	2	4	17.894	9356500	7492200	0	7053000

CBFA2T3	1	2	2	2	14.09	8417800	6259700	4725900	4383600
IFI3	3	3	3	2	23.588	4574700	5509100	7544000	6115300
EWSR1	2	2	2	2	20.357	6751700	6736200	6220000	3770000
ATP5A1	3	2	2	3	10.762	8381200	9394400	0	5654300
VPS35	2	2	2	2	5.4902	5433400	5954300	5189900	6539700
ZC3H11A	3	2	3	2	11.497	7355100	0	10238000	5049500
CARM1	1	2	2	2	25.599	0	8360600	6480200	7559000
GLYR1	4	4	3	4	13.244	4797600	5630500	5781800	6061000
EDF1	2	2	1	2	24.219	9897400	5807500	0	5803800
TIMELESS	2	2	2	2	8.9968	6720700	4574800	5008500	4886000
CAPZA2	2	2	2	1	9.26	7667200	6587700	6858900	0
EIF3D	3	3	3	2	6.8602	8654500	6401400	5882400	0
ATIC	2	3	2	3	10.453	4924800	5768900	4470700	5731900
RCC1	2	2	1	2	32.793	7218300	4720700	0	8326900
SURF6	3	3	5	3	22.416	3066000	3470000	9510600	4181800
STRAP	2	2	2	2	2.8298	5315900	5245600	3239200	6242000
FERMT3	3	3	3	3	10.311	5068500	5584400	3471500	5572700
NIPBL	1	4	2	3	13.406	0	9412900	0	10210000
EHMT2	2	2	2	2	9.8601	5201500	4041600	4790200	5509400
RUNX1	2	2	2	2	2.8427	5467600	4550900	5002000	4384000
SMARCE1	2	3	2	2	18.128	8767300	5186000	0	5206900
RAVER1	2	2	2	2	9.3619	6787300	4479900	4567000	3138700
SLTM	1	2	3	3	23.595	0	5953000	8414500	4505300
SUPT6	2	2	2	2	9.717	5043100	3413000	5691600	4480300
EIF3A	2	3	2	2	9.4737	0	9742900	0	8863600
NUDCD2	2	3	2	3	5.5009	5468400	3766500	3954100	5041500
CCT3	2	4	3	4	14.215	4667500	4911500	3449500	4802300
DEK	2	1	2	2	5.9728	4834400	0	5017800	7701900
DDX1	2	3	1	4	14.99	5743400	6194100	0	5610000
SF3B1	3	5	1	4	11.177	4458300	6534600	0	6073700
CDC40	2	2	2	1	7.4906	4203200	6170300	6250000	0
POLA1	2	2	2	2	4.8681	4711300	3628600	3331200	4943600
SF3A3	2	2	1	1	11.299	8606900	7706500	0	0
ZMYM4	1	2	2	2	8.8896	0	5298500	5468300	5452700
PFN1	3	3	3	3	8.4939	3118900	5194800	2210600	5563100
LUC7L	2	2	2	2	5.8564	3249200	3650900	3764600	5352900
ARPC3	2	3	2	3	7.8938	0	7424000	0	7984400
EEF1G	1	2	2	2	19.279	0	5343900	4049200	5910400
PCNP	3	3	3	3	3.8173	0	6158100	8736400	0
TPX2	2	1	3	2	11.65	4531900	0	4752000	5317700
CORO1B	1	2	1	2	5.9153	0	6947500	0	7380400
SSRP1	2	3	1	2	5.8708	5482200	3636200	0	5176600
SNRNP200	2	4	3	4	14.096	5475100	4326200	0	4426900
RBM17	1	2	2	2	23.731	0	4072400	4275500	5768100
SBNO1	2	2	2	2	3.3114	4728000	4307900	0	5031000
MOB1A	2	1	2	1	5.9842	6642300	0	7308700	0

CDCA5	2	2	3	3	14.927	4207600	3482000	2855600	3398300
NCOA5	1	2	2	2	12.33	0	4462500	4295400	5183200
CCT7	2	2	1	2	7.8041	4811300	4907700	0	4175100
DNMT1	3	3	4	4	4.8695	3957800	4057500	3355200	2464300
GTF2B	3	2	3	2	3.6347	4981000	4466400	0	4232700
PPWD1	1	2	2	1	5.4548	0	5764000	7576100	0
SEPHS1	1	2	2	2	3.5946	0	3639500	3761900	5897000
ABCE1	2	2	1	2	6.2228	4013000	4781500	0	3769900
TOMM34	2	2	2	3	6.8861	0	3519900	4977300	3960300
INPP5D	2	2	1	2	2.4235	4864300	3889200	0	3539200
SMARCA4	1	2	2	2	12.534	0	3398600	0	8625600
API5	2	2	2	3	11.631	0	5699200	0	6277600
SEC61B	2	2	2	1	3.8373	3796200	4284000	3425100	0
EIF3K	2	2	2	2	5.5491	3960200	2513400	2458600	2461100
MAPK1	2	2	2	1	6.3574	4964400	3399500	3024700	0
USP10	2	2	1	2	12.316	4924300	0	0	6200600
WTAP	1	2	3	3	8.7927	0	2574900	5365400	2864200
ERG	2	2	2	1	8.1984	5950100	4811200	3960300	0
RBM27	2	2	1	2	2.4361	3473400	2883500	0	4169400
GNL2	2	2	2	3	11.805	2260300	2211800	3421000	2605800
ACTR3	3	3	1	2	12.046	5123300	5197100	0	0
EIF5B	1	2	2	2	4.4406	0	4253300	0	6014700
PGLS	2	2	2	2	4.818	2763600	2708900	2000000	2793900
SAFB	2	1	3	3	12.746	0	0	5146200	4716600
PDCD2	1	2	2	2	10.071	0	2877900	3550100	3407400
CCAR1	3	2	1	1	9.5388	4822500	4505900	0	0
ATAD3A	1	2	1	2	13.007	0	3811700	0	5029300
EHMT1	2	1	2	2	2.0624	4642900	0	4097900	0
PRPF31	1	2	2	2	8.6185	0	2477500	2922600	3337800
PGAM1	1	2	2	2	4.9112	0	4369000	0	4105800
MRPS5	1	1	2	2	5.5503	0	0	4048800	4197300
PININ	2	1	2	2	5.6792	0	0	0	8161200
RANGAP1	1	2	2	1	21.965	0	3887500	4162500	0
EBNA1BP2	2	2	1	2	8.6452	3141200	0	0	4838600
CHMP4B	1	2	2	1	6.9487	0	3858900	3757000	0
UTP20	2	1	2	2	6.483	0	0	4863900	2605300
GPX1	1	2	2	1	5.6122	0	0	7430800	0
EIF2S1	2	1	2	1	4.1846	4000300	0	3304600	0
TBL3	1	2	2	2	8.0155	0	2389500	2738400	2169600
SLU7	2	1	2	2	9.9771	3398600	0	1969200	1685600
METTL1	2	2	2	2	2.3332	1735600	1304500	2120100	1598700
HNRNPUL2	1	2	1	2	10.225	0	0	3097600	3488900
MBD3	1	2	1	2	3.4622	0	3539200	0	2966300
RBM7	2	1	2	2	5.5325	6444500	0	0	0
PIN4	2	2	2	2	3.3276	6430200	0	0	0
VASP	1	2	1	2	5.5268	0	3302700	0	3082200

SUPT5	1	2	1	2	8.2113	0	2831400	0	3544000
RPA1	1	2	2	3	5.2017	0	0	0	5828200
DDX19A	2	2	1	2	6.7585	2659100	2685200	0	0
NSUN2	3	1	1	2	4.6193	0	0	0	4913500
PTPN6	1	2	2	1	3.5284	0	2408500	2326500	0
DDX52	1	1	2	2	11.628	0	0	2432700	1946300
ESCO2	3	3	1	2	8.8267	0	0	0	3661400
RFC1	2	1	2	1	5.8929	0	0	2401900	0
KLF13	3	2	2	3	10.762	6394400	0	0	5154300
YY1	2	3	2	2	14.927	0	9510600	0	3639500

Table S3: Related to Figure 4 - Overrepresentation PC1-specific analysis to demonstrate erythroid differentiation specificity

p-value	q-value	pathway	source
2.31E-07	3.17E-05	hemoglobins chaperone	BioCarta
2.24E-06	0.000153136	Hematopoietic Stem Cell Differentiation	Wikipathways
6.60E-06	0.000226049	heme biosynthesis	HumanCyc
6.60E-06	0.000226049	Heme Biosynthesis	Wikipathways
1.29E-05	0.000350508	Heme biosynthesis	Reactome
1.54E-05	0.000350508	Transcriptional misregulation in cancer - Homo sapiens (human)	KEGG
2.70E-05	0.000463082	Ferroptosis - Homo sapiens (human)	KEGG
2.70E-05	0.000463082	Ferroptosis	Wikipathways
7.38E-05	0.001123376	Metabolism of porphyrins	Reactome
0.000187498	0.002568719	tetrapyrrole biosynthesis	HumanCyc
0.000329785	0.004107327	Activation of Matrix Metalloproteinases	Reactome
0.000391528	0.004469944	Porphyrin metabolism	INOH
0.000667413	0.007033511	Erythrocytes take up oxygen and release carbon dioxide	Reactome
0.000813954	0.007965123	Porphyrin and chlorophyll metabolism - Homo sapiens (human)	KEGG
0.001213284	0.010882721	Iron metabolism in placenta	Wikipathways
0.001278231	0.010882721	Malaria - Homo sapiens (human)	KEGG
0.001429847	0.010882721	Erythrocytes take up carbon dioxide and release oxygen	Reactome
0.001429847	0.010882721	O2/CO2 exchange in erythrocytes	Reactome
0.001786609	0.010925639	Copper homeostasis	Wikipathways
0.001913981	0.010925639	Hereditary Coproporphyrinuria (HCP)	SMPDB
0.001913981	0.010925639	Porphyria Variegata (PV)	SMPDB
0.001913981	0.010925639	Congenital Erythropoietic Porphyria (CEP) or Gunther Disease	SMPDB
0.001913981	0.010925639	Acute Intermittent Porphyria	SMPDB
0.001913981	0.010925639	Porphyrin Metabolism	SMPDB
0.002181256	0.011953285	ID signaling pathway	Wikipathways
0.002465142	0.012508315	ACE Inhibitor Pathway	Wikipathways
0.002465142	0.012508315	Metabolism of Angiotensinogen to Angiotensins	Reactome
0.002579494	0.012621097	Adipogenesis	Wikipathways
0.003082163	0.014075209	Hematopoietic Stem Cell Gene Regulation by GABP alpha-beta Complex	Wikipathways
0.003082163	0.014075209	prion pathway	BioCarta
0.003415008	0.014620504	ACE Inhibitor Pathway, Pharmacodynamics	PharmGKB
0.003415008	0.014620504	Agents Acting on the Renin-Angiotensin System Pathway, Pharmacodynamics	PharmGKB
0.003853395	0.015997427	p53 signaling pathway - Homo sapiens (human)	KEGG
0.004240205	0.017085532	SLC-mediated transmembrane transport	Reactome
0.004509175	0.017650198	Renin-angiotensin system - Homo sapiens (human)	KEGG
0.005743831	0.021267698	Basigin interactions	Reactome
0.005743831	0.021267698	ID	NetPath
0.006130637	0.022102559	TGF-beta signaling pathway - Homo sapiens	KEGG

(human)

0.008034209	0.028222735	Transport of small molecules	Reactome
0.008573078	0.028802499	Hematopoietic cell lineage - Homo sapiens (human)	KEGG
0.008619726	0.028802499	Development and heterogeneity of the ILC family	Wikipathways
0.009193396	0.029987983	Extracellular matrix organization	Reactome
0.009694874	0.030888318	Porphyrim metabolism	EHMN

Supplemental figure legends

Figure S1

A. Box plots with 10-90 percentiles of Stag2, Smc3, Smc1a and Stag1 expression in the indicated populations. Erythroid and Myeloid progenitors were empirically considered as all cells with normalized expression of Klf1 > 10 and Spi1 > 10, respectively.

B. Schematic representation of the defining criteria for cis-regulatory element classification.

C. Density heat map of Rad21, Ctfc, Pol2 and the chromatin marks H3K4me3, H3K27ac and H3K4me1. Peak classification was defined based on the Figure S1B schema.

D,G. Plots of normalized Smc1 and Ctfc binding ratio ($\text{Smc1_in_erythroid}/\text{Smc1_in_HPC}$ and $\text{Smc1_in_myeloid}/\text{Smc1_in_HPC}$ for (D), $\text{Ctfc_in_erythroid}/\text{Ctfc_in_HPC}$ and $\text{Ctfc_in_myeloid}/\text{Ctfc_in_HPC}$ for (G)) at Cohesin-associated active enhancers, active promoters and insulators/others in the HPC, erythroid and myeloid cellular stages. Shown are means with SD of replicated experiments.

E,H. Total count of significant differentially bound Smc1 (E) and Ctfc (H) peaks in the HPC to Erythroid differentiation (upper panels for each figure) and the HPC to myeloid differentiation (lower panels - missing for Smc1 because no peak reached the threshold of significance). Left panels show pie charts of genomic location of differential bound peaks. Scatter plots (right) - representation of the differential Smc1 (E) and Ctfc (H) binding at active promoters and enhancers in the indicated populations. Blue dots (Lost) show peaks that decrease, while red/purple dots (Gained for erythroid and myeloid respectively) show peaks that increase during the specified differentiation.

F. Immunoblotting of Stag2, Rad21 and Actin protein expression in HPC, Erythroid and Myeloid cells.

Figure S2

A. Normalized enrichment scores (NES) for the top 5 hematopoiesis-related datasets that differed between Erythroid and Immature genes, as determined by GSEA. FDRq values were < 0.001 in all datasets. Input was a ranked list of all $p_{adj} < 0.1$ genes from Figure 2F.

B. Average profiles of Rad21 and H3K27ac binding at promoters of erythroid (red lines) and immature (blue lines) genes.

C. Box plots and 10-90 percentiles of the differences between significant interactions of baits at promoter regions of erythroid genes (red) and immature genes (blue) in the Erythroid and HPC cellular states. Interactions were outputted with the CHICAGO pipeline. The threshold for significance was set at 5.

Figure S3

Spring viewer plot displaying scRNASeq expression of Etv6 during the murine hematopoiesis. Minimum value = black, maximum value = neon green.

Figure S4

A. Inducible knockdown of the indicated Cohesin members in HPC after 72 hours of Dox-induction. Shown are 4 experimental replicates for each KD clone, with the exception of shR21_3, where experiments were only repeated 3 times. Comparison and calculation of degree of knockdown internally was made with 4 experimental replicates of three different Luc clones.

B. Immunoblotting of the indicated proteins demonstrates KD efficiency.

C. Similar to Figure 4B, plots of normalized protein binding ratios at the indicated genomic regions. Ratio was performed as $\text{shCohesin}_{\text{HPC}}/\text{Luc}_{\text{HPC}}$. To minimize global quantitative biases, the binding signal was CPM normalized and internally calibrated to the signal at insulators/other sites (see Materials and methods). Shown are means of replicated biological experiments.

D. Similarly to Figure 4C, differential gene expression between Luc_HPC and shR21_HPC, and Luc_HPC and shS1a_HPC. The blue shaded area consists of genes enriched in HPC, while the grey shaded area shows genes significantly expressed in shCohesins_HPC. The numbers at the upper corners show the counts of $\log_2FC > 0.5$, $p_{adj} < 0.1$ and ($\log_2FC > 1$, $p_{adj} < 0.05$) significant differential genes. The significance and difference spreads were set intentionally to match those in Figure 4F.

E. NES for significant hematopoiesis-related datasets that were generated by GSEA. Input was a ranked list of all $p_{adj} < 0.1$ genes from the corresponding Figures 4C and S4D datasets.

F. Counts of CD71, CD71/Ter-119 and Ter-119 positive cells in the indicated cell lines after 6 days of EPO induction.

G. Representative flow cytometric analysis of myeloid differentiation following IL-3 for Luc_Myelo and shS2_Myelo at the indicated times.

H. Counts of CD11b, CD11b/CD14 and CD14 positive cells in the indicated cell lines after 6 days of IL-3 induction.

Figure S5

A. Differential binding of Rad21 at Tier1 promoters in Luc-Ery and shS2-Ery cells was displayed in a waterfall plot to visualize the high variability of the binding differences between the 2 groups.

B. and C. “Lost” promoter regions from Figure 5D (enriched in Luc_ery, lost in shS2_ery) were annotated with the GREAT platform. Shown are $-\log_{10}$ binomial FDR q-values for the 10 most significant terms of the GO biological processes (B) and MGI phenotype (C) enrichments.

D. - F. Plots of - D. - differential genes in Luc_ery and shS2_ery cells, - E. - H3K27ac at the promoters of differential genes, - F. - interaction frequency of promoters of differential genes – all correlated with Rad21 binding at the corresponding regions. All values are means from replicate biological experiments.

G. Example of Rad21 and H3K27ac dynamics binding, as well as interaction frequencies between Luc_ery and shS2_ery at the Gata1 promoter (RNASeq $\log_2\text{foldChange} -1.7$).

Figure S6

- A. Only modest overlap is demonstrated between erythroid differentiation Tier 1 and perturbation Tier A (left panel) and the erythroid differentiation Tier 4 and perturbation Tier D (right panel).
- B. Gene expression analysis of *Etv6* after 3 and 5 days of Dox-induction in the indicated isogenic cells.
- C. Gene expression analysis of *Etv6*, recording the KD efficiency 2 days after transduction in the indicated isogenic cells (also see Materials and methods).
- D. Longitudinal testing of cell viability of Dox-induced Luc-HPC and shS2-HPC cells after transduction with control Scr or *Etv6*-directed short hairpins. Shown are results from three independent experiments.

Figure S7

- A. Gene expression differences between STAG2mut and other MDS subtypes for Luc_Ery-enriched genes from Figure 4F. Genes that were enriched in other MDS subtypes are marked with shades of red, while genes that were enriched in STAG2mut MDS were marked with shades of blue. Specific genes of interest are shown to the right.
- B. Similar analysis in AML. Gene expression differences between Cohesin mutated (18 samples) and other AML subtypes (133 samples) from the TCGA LAML dataset for Luc_Ery-enriched genes from Figure 4F. Genes that were enriched in other AML subtypes are marked with shades of red, while genes that were enriched in Cohesin mutated AML were marked with shades of blue. Differential gene expression and FDRq values were computed with DESeq2 (citation). Specific genes of interest are shown to the right.
- C. and D. Differences in expression between normal bone marrow, other MDS and STAG2mut MDS CD34+ cells (C) or other AML and Cohesin mutated AML (D) specifically at the alpha- and beta- globin genes.

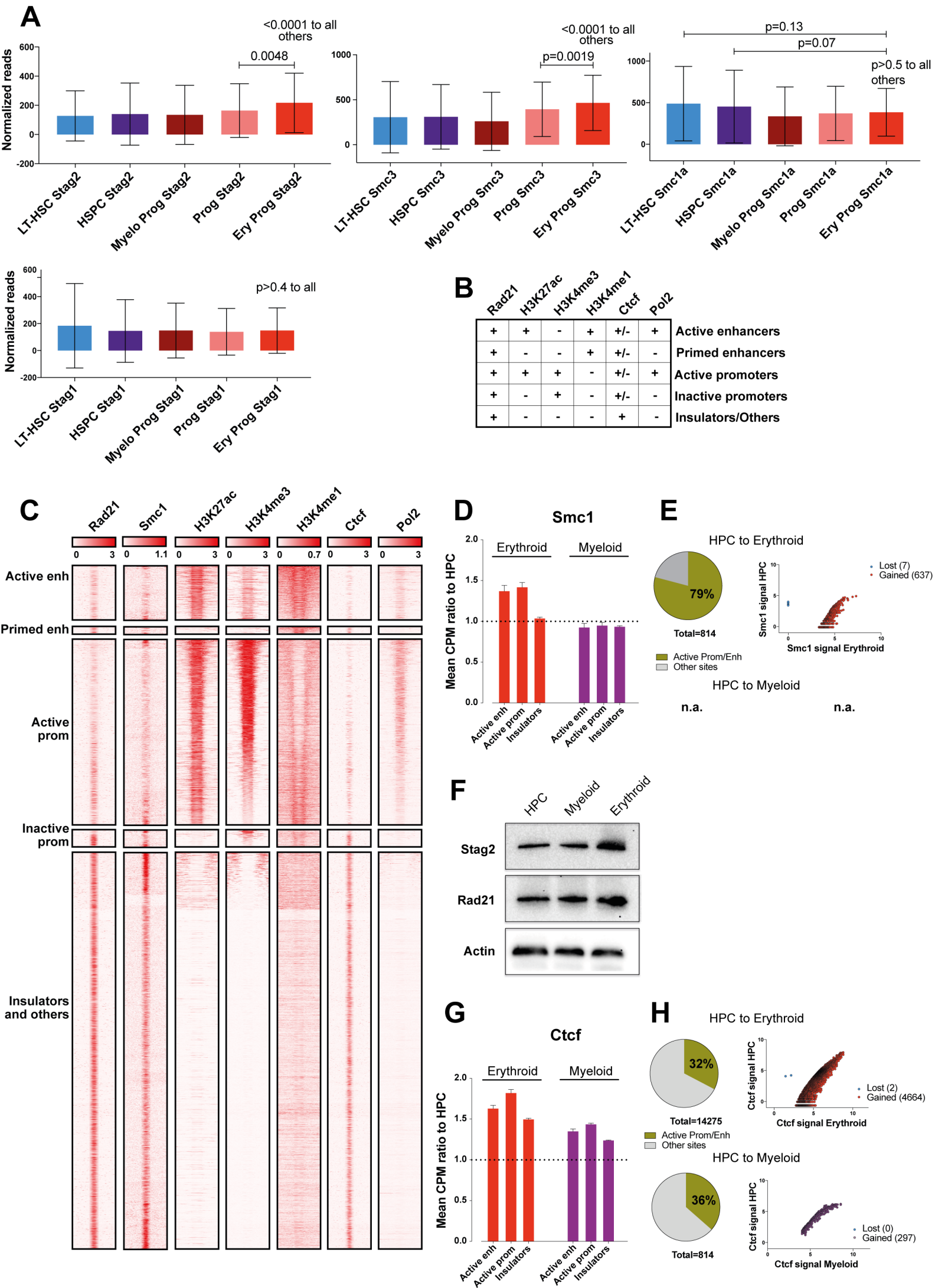


Figure S1

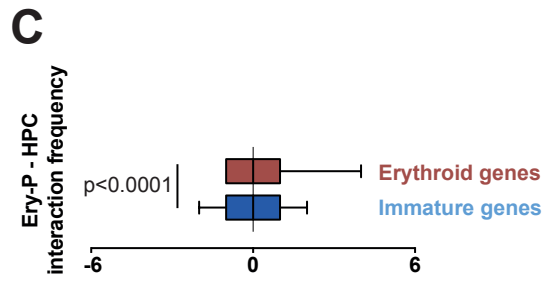
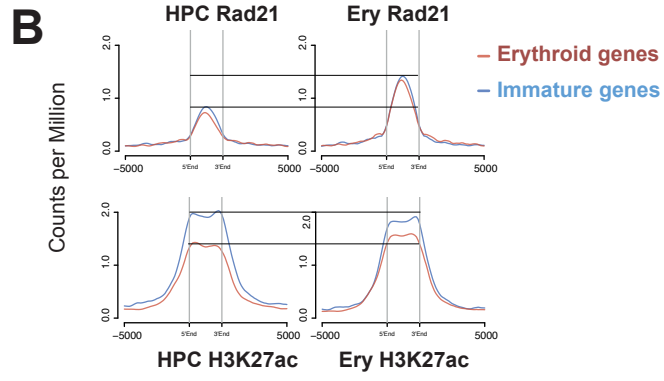
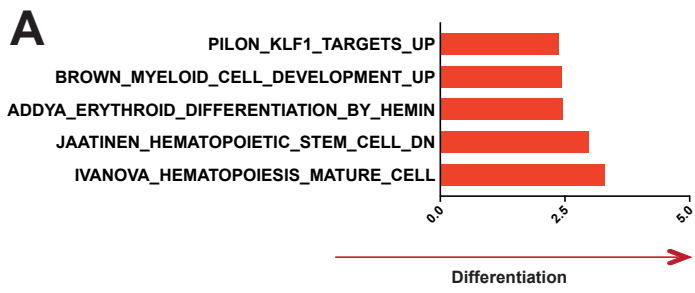


Figure S2

Etv6 expression

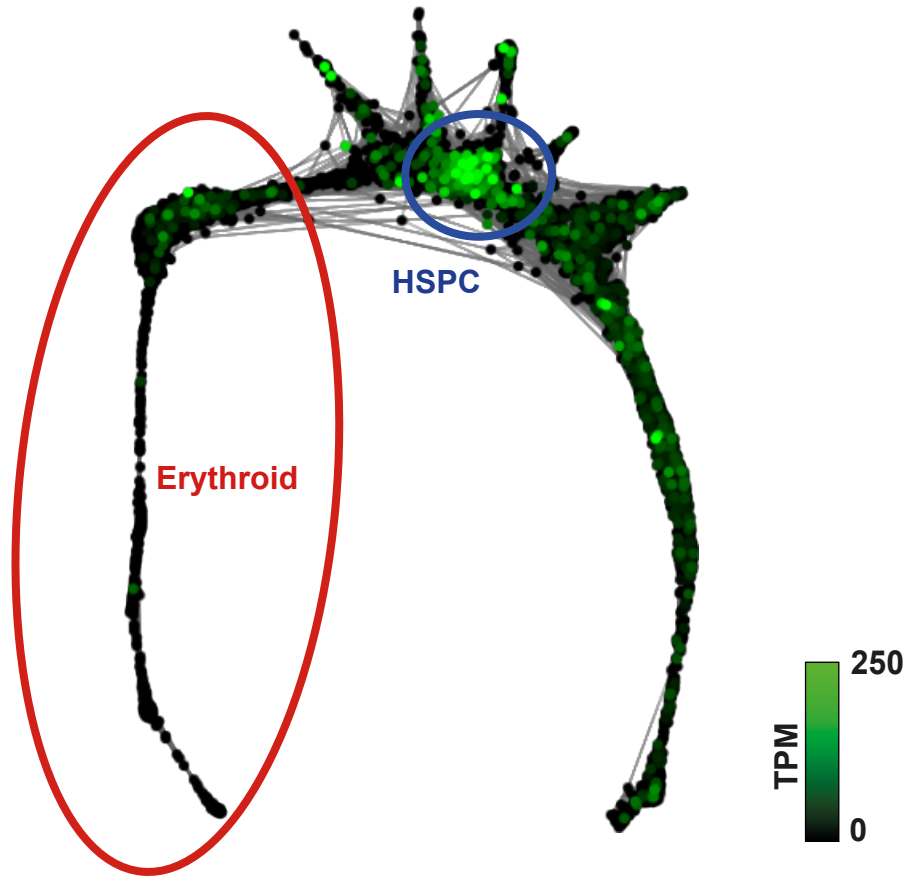


Figure S3

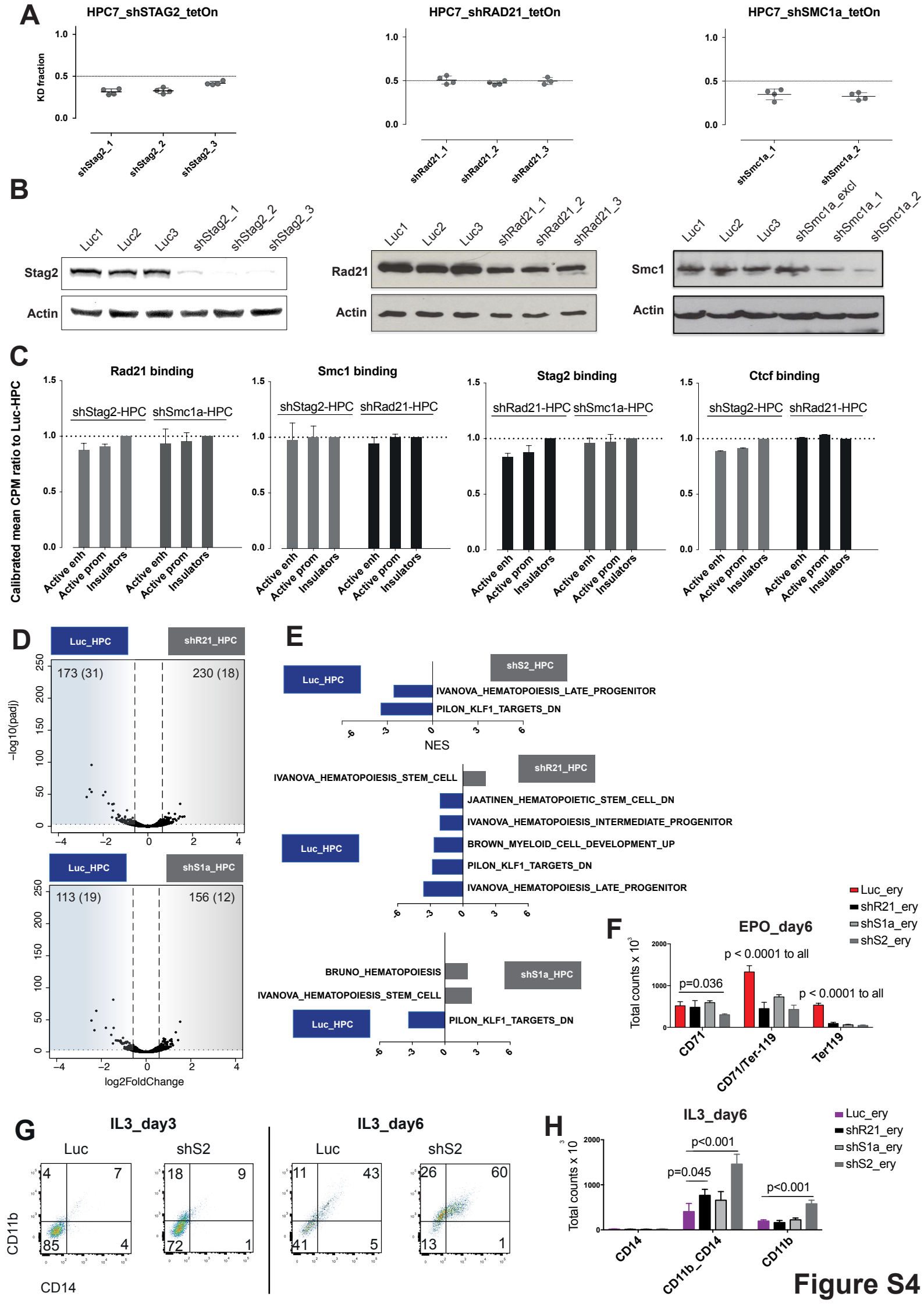


Figure S4

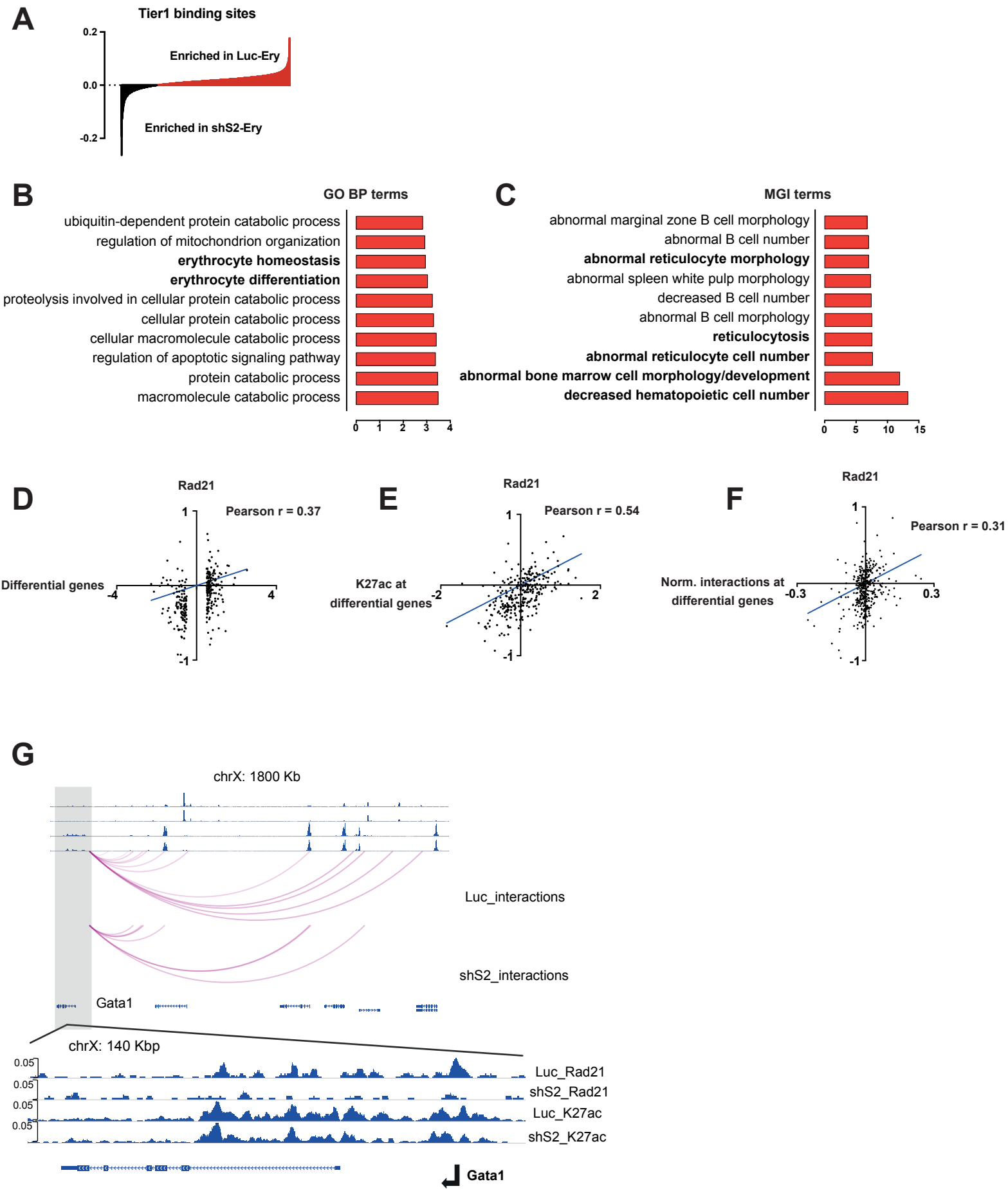
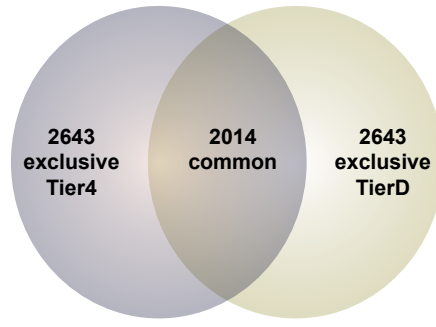
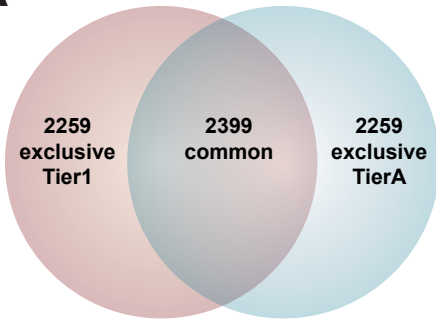
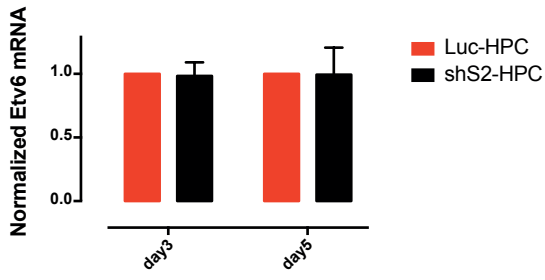
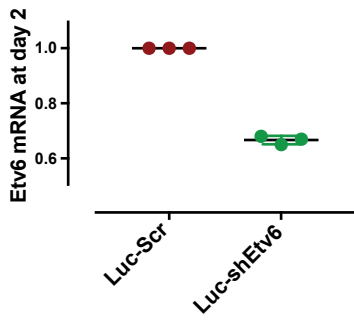
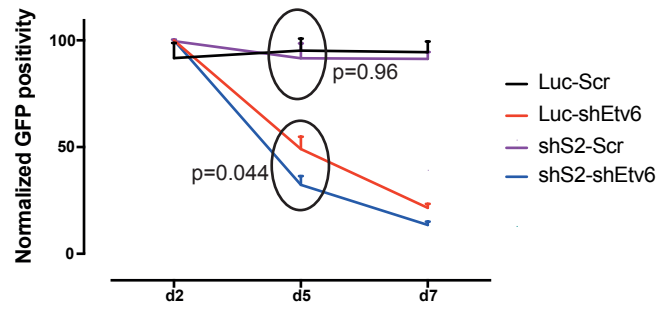
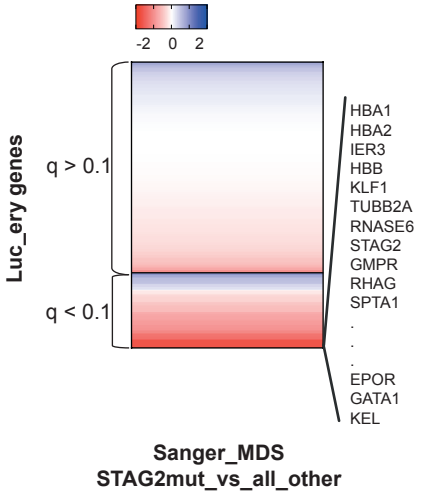
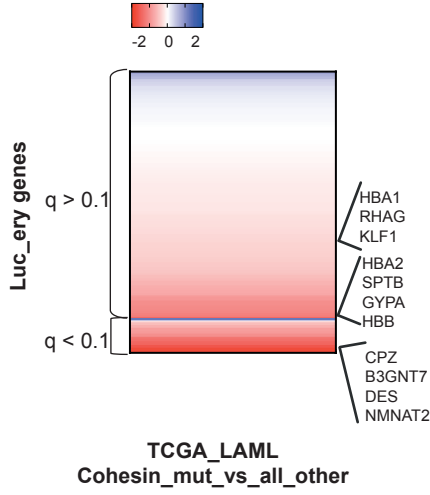
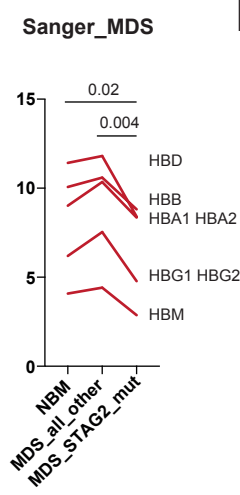


Figure S5

A**B****C****D**

A**B****C****D**