Aging-declined RNA exportation impairs hematopoietic stem cells by inducing R-loop

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Received: March 6, 2025.
Accepted: June 26, 2025.
Early view: July 3, 2025.

https://doi.org/10.3324/haematol.2025.287765

Online Supplemental Methods

Mice

Alyref$^{flox/flox}$ mice were generated in Cyagen Biosciences Inc. (Guangzhou, China). Alyref$^{flox/flox}$ mice (C57BL/6N) were generated by inserting loxP sites spanning the third exon of Alyref via homologous recombination. To achieve hematopoietic-specifically knockout mice, Alyref$^{flox/flox}$ were crossed to Mx1-Cre mice. To induce Cre expression in Mx1-Cre^{+}; Alyref$^{flox/flox}$ mice were intraperitoneally injected with Poly I:C (25 mg/kg) every other day for 14 days. All genotyping primers are listed in *Online Supplementary Table S1*.

C57BL/6 mice (CD45.2) and C57BL/6-SJL (CD45.1) mice were from the Jackson Laboratory. All of these strains were maintained on C57BL/6 background. The recipients used in the competitive transplantation assays were CD45.1/2 that were the first generation of C57BL/6 (CD45.2) and B6.SJL (CD45.1) mice. All mice were housed in specific-pathogen-free, and all procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Tsinghua University.

Hematological cell counts

PB after tail bleeding was analyzed by Auto Hematology Analyzer BC-5000 (MINDRAY). BM cells were harvested from one femur and suspended in HBSS^{+} buffer on ice before counting by Vi-CELL Cell Counter (Beckman).

Lentivirus production and transduction

The cDNA was cloned into SF-LV-cDNA-EGFP vector and the shRNA was cloned into pLKD-CMV-G&PR-U6-shRNA vector. Lentivirus was produced in 293T cells and was concentrated according to standard procedures[1]. For lentivirus transduction, 1×10^5 Lineage^{-} c-Kit^{+} Sca1^{+} (LSK) cells were sorted and plated in 96 well plate added 100 μL SFEM medium (Stem Cell Technology, 09650) with 20 μg/mL mSCF, 20 μg/mL mTPO and 1 % penicillin/streptomycin. All shRNA sequences and clone primers are listed in]*Online Supplementary Table S2*.

Transplantations and peripheral blood analysis

For the competitive HSC transplantations assay. Freshly isolated 100 HSCs（CD45.2）were injected into lethally irradiated recipient mice (CD45.1/2) together with 3×10^5

whole BM cells (CD45.1) as competitor. Recipient mice were irradiated a lethal dose of radiation (10 Gy) using X-ray irradiator (RS-2000, Rad Source Technologies) before transplantation. Regarding the secondary transplantation, 2×10^6 whole BM cells from the primary recipients were injected into the secondary recipient mice. Recipient mice were analyzed for donor-derived chimaerism (including T cells, B cells, myeloid cells) every 4 weeks. The antibodies combination (CD3, B220, CD11b, CD45.1 and CD45.2) were used to analyze PB.

For the competitive HSPC transplantations assay. 2000 GFP^+ $Sca1^+$ $CD48^-$ HSPC (CD45.2) were injected into lethally irradiated recipient mice (CD45.2) together with 3×10^5 whole bone marrow cells (CD45.1) as competitor. Regarding the secondary transplantation, 2×10^6 whole BM cells from the primary recipients were injected into the secondary recipient mice. Recipient mice were analyzed for donor-derived chimaerism (including T cells, B cells, myeloid cells) every 4 weeks. The antibodies combination (CD3, B220, CD11b, CD45.1) were used to analyze PB.

Flow cytometric analysis and cell sorting

Cells were suspended in $HBSS^+$ buffer and then stained for the fluorophore coupled antibodies. Then flow cytometry analysis data were collected from BD LSRFortessa SORP flow cytometer (BD Biosciences), and then analysed by FlowJo software. Cell sorting was performed by BD Influx (BD Biosciences) and cells were sorted into $HBSS^+$ buffer. A detailed list of antibodies used for flow cytometric analysis and cell sorting are provided in the *Online Supplementary Table S3*.

Immunofluorescence staining

Cells were centrifuged onto poly-lysine coated coverslips by Thermo Scientific Shandon Cytospin 4 (1000 rpm, 5 min), fixed with 4% PFA for 20 min at room temperature, washed with PBS for 3 times. Then cells were permeabilized in 0.5% TritonX-100 for 30 min at room temperature and blocked in 5% BSA/PBS for 1 h. Coverslips were then incubated overnight in 4℃ in 5% BSA/PBS with the following antibodies alone or in combination: anti-phospho-H2AX (Ser139) (Millipore, 05-636), anti-RPA32 (CST, 2208s), Anti-DNA-RNA Hybrid, clone S9.6 (Millipore, MABE1095). Coverslips were washed 3 times in PBST and incubated for 1 h at room

temperature in 5% BSA/PBS with appropriate secondary antibodies (Invitrogen). Coverslips were then washed 3 times in PBST and stained with DAPI (1ug/mL) for 10 min, washed with PBS for 3 times. Cells were observed under a FV1200 confocal microscope (Olymplus), using a 100 × objective.

For in vitro RNase H or RNase III treatment, cells were treated with RNase H (New England Biolabs, M0297S) for 2 h or ShortCut RNase III (New England Biolabs, M0245L) for 20 minutes at 37˚C after 0.5% TritonX-100 permeabilization before 5% BSA blocking. A detailed list of antibodies used for Immunofluorescence staining are provided in the *Online Supplementary Table S4*.

RNA fluorescent in situ hybridization

RNA FISH was conducted using a Ribo fluorescence in situ hybridization kit (RiboBio, C10910) in accordance with the manufacturer's directions. In brief, cells were centrifuged onto poly-lysine coated coverslips by Thermo Scientific Shandon Cytospin 4 (1000 rpm, 5min), fixed with 4% PFA for 10 min at room temperature, washed with PBS for 3 times. Then cells were permeabilized in 0.5% TritonX-100 for 30 min at 4℃, washed with PBS for 3 times. Then Pre-hybridization buffer was added at 37°C for 30 min. Hybridization was carried out with a Cy3-labelled oligo $(dT)_{50}$ probe at 37°C in the dark overnight. The coverslips were washed 3 times with Wash Buffer I, once each with Wash Buffer II and Wash Buffer III at 42℃ in the dark and once with PBS for 5 min at room temperature. Then cells were stained with DAPI (1μg/mL) in the dark for 10 min, washed with PBS for 3 times. Cells were observed under a FV1200 confocal microscope (Olymplus), using a 100 × objective.

For the R-Loop and mRNA co-localization assay, cells were performed for RNA FISH after cells incubated by Anti-DNA-RNA Hybrid, clone S9.6 and secondary antibodies.

Quantitative real-time PCR

Total RNA was extracted using TRIzol (Invitrogen, 15596018) according to the manufacturer's Instructions. Total RNA was subjected to reverse transcription using PrimeScript™RT reagent Kit with gDNA Eraser (Takara, RR047A). Acquired cDNA was analyzed by PowerUp SYBR Green mix (Applied Biosystems, A25780) on

QuantStudio-3 Real-time PCR System (Applied Biosystems). The primer information is listed in *Online Supplementary Table S5*.

Western blot

Freshly isolated $CD34^-$ LSK cells were lysed in sodium dodecyl sulfate (SDS) loading buffer, lysis was completed by sonication and denatured by boiling. Samples were resolved by 10% SDS-PAGE. PVDF membranes were blocked by 5% skim milk in Tris-buffered saline with Tween-20 buffer and then incubated with indicated primary and second antibodies. A detailed list of antibodies used for Western blot are provided in the *Online Supplementary Table S4*.

DNA fiber assay

Freshly isolated $CD34^-$ $Flt3^-$ LSK cells were cultured for 36 h, then pulsed for 38 min with 50 μM CIdU (TargetMol, T19151), washed twice with PBS, and then pulsed for 38 min with 250 μM IdU (TargetMol, T0863). Labeled cells were resuspended in ice-cold PBS at 1000 cells per microlitre. 2.5 μL cell resuspension was spotted onto a glass slide and lysed with 7.5 μL of spreading buffer (0.5% SDS in 200 mM Tris-HCl pH 7.4, 50 mM EDTA). Slides were tilted at an angle of 15° to 30° to allow the droplet run down slowly and at a constant speed. Then the slides were air-dried for 15 min, fixed in 3:1 volume absolute methanol: glacial acetic acid for 20 min and air-dried. DNA was denatured with 2.5 M HCl overnight at 4℃, washed twice with PBS and blocked with 1%BSA in PBS for 1h at room temperature and incubated with rat anti-CIdU/BrdU (Abcam, ab6326) and mouse anti-IdU/BrdU (Becton Dickinson, 347580) antibodies for 3h at room temperature to detect CIdU and IdU respectively. Then slides were washed with PBS and incubed for 2 h at room temperature with A488-conjugated goat anti-rat (Invitrogen, A-11006) and A594-conjugated goat anti-mouse (Invitrogen, A-11005) secondary antibodies. Images were observed under a FV1200 confocal microscope (Olymplus), using a 60 × objective. The length of CIdU and IdU tracks was measured using ImageJ software.

Cytoplasmic and nuclear RNA fractionation and sequencing

Freshly isolated $CD34^-$ LSK cells were lysed in 20 μL cold cytoplasmic lysis buffer (0.15% NP-40, 10 mM Tris-HCl pH 7.5, 150 mM NaCl). The lysate was layered onto

50 μL cold sucrose buffer (10 mM Tris-HCl pH 7.5, 150 mM NaCl, 24% sucrose), and centrifuged in microfuge tubes at 16000 × g for 10 min. The supernatant from this spin represented the cytoplasmic fraction, and the pellet represented the nuclear fraction. Then, 3.5 × volume TRIzol was added to the supernatant for cytoplasmic RNA purification, and an equal volume of TRIzol was added to the pellet for nuclear RNA purification. The cytoplasmic and nuclear fractions were used to generate cDNA libraries sequenced with 150-bp paired-end reads on an Illumina instrument by Novogene.

ssDRIP-seq and ssDRIP-qPCR

ssDRIP-seq library construction was performed according to published procedures [1]. Briefly, freshly isolated $CD34^-$ LSK cells were resuspended in DNA lysis buffer (10 mM Tris-HCl pH 8.0, 1 mM EDTA pH 8.0, 0.5% SDS, 0.1 mg/mL Proteinase K), incubated at 37°C in a shaker with 180~240 rpm for 4~6 h. The extracted genomic DNA was fragmentated using a cocktail of restriction enzymes (MseI, DdeI, AluI and MboI, New England Biolabs). The negative control was treated with RNase H (New England Biolabs, M0279S). DRIP was performed with the commercial S9.6 antibody (Millipore, MABE1095). Then the DRIPed DNA was validated by qPCR or sonicated into the size of 250 bp using Covaris S220 with 10% duty factor, 175 W, 200 cycles per burst, and 2 min treatment time. The ssDRIP-seq libraries were constructed from the sonicated DNA using VAHTS® ssDNA Library Prep Kit for Illumina (Vazyme, ND620-C), following instructions from the manufacturer. The libraries were checked on a fragment analyzer, followed by sequencing on an Illumina NovaSeq system.

dCas9 coupled RNaseH1 D209N-mediated site-specific R-Loop

dCas9 coupled RNaseH1 D209N-mediated site-specific R-Loop was performed according to published reference [2]. In brief, dCas9 infused with RNaseH1 D209N was co-expressed with gRNA targeting the selected R-Loop sites in NIH-3T3 cells. $mCherry^+$ cells were purified for ssDRIP-qPCR and Immunofluorescence staining. The gRNA and qPCR primers are listed in *Online Supplementary Table S6*.

RNA-seq

In brief, 50 HSCs were sorted directed into lysis buffer. Then the RNA-seq library

was prepared using the method of Smart-seq2. After the library construction, assess the insertion size by Agilent Bioanalyzer 4200 system (Agilent Technologies), and quantify the accurate insertion size by Taqman fluorescence probe of AB Step One Plus Real-Time PCR system. Perform the clustering of the index-coded samples using HiSeq PE Cluster Kit v4-cBot-HS (Illumina) following the manufacturer's instructions. The libraries were sequenced by an Illumina Hiseq platform with 150-bp paired-end. The transcriptome sequencing was performed by ANNOROAD Gene Technology Company.

RNA-seq data processing

TrimGalore software (v0.6.6) (https://github.com/FelixKrueger/TrimGalore) was performed to remove adaptor, low quality base for raw reads and FastQC (v0.11.9) was used to do quality control check. Trimmed reads were then mapped to the mouse reference genome (Ensemble GRCm38) by STAR (v2.7.10 b), raw read counts and TPM (Transcripts Per Million mapped reads) of genes were quantified with RSEM (v1.3.1). R-package DESeq2 was performed to normalize gene counts and infer the differential expression levels of samples between two different groups.

Public RNA-seq data meta-analysis

Five public RNA-seq data sets were collected from GEO and ArrayExpress database. GSE70657 and GSE87631 were scRNA-seq (single cell) data of HSCs, raw read counts of which were normalized by using ZINB-WaVE. The other three datasets were normalized through DESeq2 method. For each dataset, DESeq2 was performed to get the differential expression levels between young and aged HSCs. 6073 genes expressed in all the five datasets were left in the following meta-analysis. Fisher's combined p-value and median of log2 fold change were obtained for each gene. 763 genes with Bonferroni corrected p-value < 0.05 and median (log2 FC) < 0 were identified as down-expressed genes in aged HSCs.

RNA-seq data analysis

RNA-seq reads were processed as described above. Samples of Alyref$^{+/-}$ and Alyref$^{-/-}$ HSCs were compared to WT HSCs through DESeq2, separately. The statistics value from DESeq2 was used as input to perform the pre-ranked GSEA.

Cytoplasmic and nuclear RNA-seq data analysis

Raw sequencing reads were processed as described above and TPM for each gene was obtained. Average log2-transformed TPM of replicates was calculated for each fraction and sample. Nucleus/Cytoplasm (Nuc/Cyto) ratio was used to quantified as RNA localization for young or aged sample.

ssDRIP-seq data processing

TrimGalore (v0.6.6) was conducted to remove adaptor sequences and to trim 10 bases on both ends for all files of raw reads. Reads with less than 50 bases were filtered out. Then, the trimmed reads were aligned to the mouse reference genome (ENSEMBL GRCm38) using Bowtie2, with "--local" parameters. Duplicated reads were removed by Picard tools (v2.26.3) (https://broadinstitute.github.io/picard). Reads with mapping quality more than 10 were remained and sorted, then was separated into forward (Watson strand) and reverse strand (Crick strand) using SAMtools. Reads of replicates for each kind of samples were merged for the subsequent analysis.

RPGC (Reads Per Genome Coverage)-normalized signal across whole genome were obtained, and log-transformed ratio of RPGC-normalized R-Loop signal and input were calculated by deepTools (v3.5.1). We draw metaplot of comparative normalized R-Loop signal of aged and young samples on the genebody region and peak summits.

R-Loop peak calling

Strand-specific peaks were called by MACS3 (v3 3.0.0b1) with R-Loop and input samples. Peaks with q values less than 0.01 and enrichment score more than 10, and located outside the blacklisted region were defined as R-Loop peaks. We annotate peaks with genomic regions by R package ChIP seeker.

Differential analysis of R-Loop signals in genebody and its regulatory region

In our study, genebody and its regulatory region was defined as from 2000 bp upstream of TSS (transcription start site) to 2000 bp downstream of TES (transcription end site), and genebody region as from the TSS to TES. For each gene, read coverage on these two regions of ssDRIP-seq reads were counted by deepTools (v3.5.1) in young and aged samples. DESeq2 R package was used to normalize the

raw reads count and estimate the difference of R-Loop signal between young and aged samples. DESeq2 statistics of R-Loop reads on the genebody region was used as input to perform pre-ranked GSEA. According to the quantiles of DESeq2 statistics of R-Loop reads on the genebody and its regulatory region, genes were grouped into four levels with different R-Loop difference (level 1 < -0.53583 < level 2 < 0.01050 < level 3 < 0.56268 < level 4). To investigate the relationships of RNA localization and R-Loop signals of genes, we compared the ratios of RNA localization (Nuc/Cyto ratio) in young and aged samples of genes in different levels defined above.

Whole-genome sequencing and data processing

Freshly isolated 1×10^6 LSK cells were extracted using the HiPure Blood DNA Mini Kit (Magen, D3111-03), according to the manufacturer's instructions. After DNA libraries construction and quality control, sequencing was performed using BGISEQ sequencing platform. Raw reads were trimmed using TrimGalore (v0.6.6). Then, cleaned reads were aligned to the mouse reference genome (ENSEMBL GRCm38) by BWA, low mapping quality reads and duplicates were removed by Picard tools (v2.26.3). The InDels of young and aged samples were called by HaplotypeCaller in GATK tools (v4.0.5.1). The whole-genome sequencing and data analysis were performed by BGI.

Gene ontology enrichment analysis and gene set enrichment analysis

R package ClusterProfiler was used to make enrichment analysis on BP (Biological Process) GO. Pre-ranked GSEA was conducted on collected gene sets to make the gene set enrichment analysis.

Statistical Analysis

Statistical analysis was made using the Prism software (Prism, GraphPad Software Inc., San Diego, CA USA). Data are shown as mean ± SD. Student's *t* test (Two-tailed unpaired) were used for comparisons (GraphPad Prism v.7.0). ns, not significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. All experiments were repeated 2 or 3 times independently.

Data availability

RNA-seq, cytoplasmic and nuclear RNA sequencing**,** ssDRIP-seq data have been

deposited in the GEO (Gene Expression Omnibus). The accession code is GSE239301. Whole Genome sequencing data have been submitted to SRA (Sequence Read Archive), and the BioProject accession is PRJNA1000120. Further information and requests for resources and reagents should be directed to and will be fulfilled by the Contact, Dr. Jianwei Wang (wangjianwei@ihcams.ac.cn).

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Online Supplementary figures

***Online Supplementary Figure S1*. R-Loop is increased in aged hematopoietic stem cells, related to Figure 1.**

(A) Experimental design of ssDRIP-seq. Freshly isolated 5×10^4 HSCs ($CD34^-$ LSK) from young (2 months old) and aged mice were subjected to ssDRIP-seq.

(B) Metaplot of RPGC-normalized R-Loop signals located between 2 kb upstream of the transcription start site (TSS) and the downstream region of the transcription end site (TES) for all genes with R-Loop reads.

(C) Metaplot of RPGC-normalized R-Loop signal located between 1 kb upstream and 1 kb downstream of the peak summits.

(D) Boxplot of the width of the R-Loop peaks separately obtained in young and aged HSCs (one-sided Wilcoxon signed rank test).

(E) Pre-RANKED GSEA of cell aging-related genes and myeloid cell differentiation-related genes with R-Loop signal differences between young and aged HSCs. The genes were ranked according to the DESeq2 statistics after comparing ssDRIP reads in the region corresponding to the gene body in aged versus young samples. NES, normalized enrichment score; FDR q-values are provided. $|NES|>0.3$ and $q<0.05$ represent statistically significant differences.

***Online Supplementary Figure S2*. Accumulated R-Loop induces DNA damage and impairs the function of hematopoietic stem cells, related to Figure 2.**

(A) Representative fluorescence images depicting the co-localization of the R-Loop with RPA in aged HSCs.

(B) Schematic of the strategy employed to introduce R-Loop to specific regions.

(C) Representative western blot showing the knockdown efficiency of shRNA against RNaseH1 and RNaseH2A using freshly isolated LSK cells.

(D) Line plots depicting the proportion of donor-derived cells (Overall, B cells, T cells, myeloid cells) in the peripheral blood of recipients. n=6 recipients per group. The data are presented as mean ± SD.

(E) Dot plots depicting the lineage distribution of donor-derived peripheral blood cells at the 12^{th} week of recipients. n=6 recipients per group. Data are presented as mean ± SD.

(F) The dot plot displays the percentage of donor-derived cells (Overall, T cells, B cells, myeloid cells) in the bone marrow of recipients at the conclusion of the 12^{th} week. Each group comprises n=6 recipients, and the data are presented as mean ± SD.

(G) The dot plot demonstrates both the number and the percentage of HSCs in the whole bone marrow of recipients at the conclusion of the 16^{th} week. Each group comprises n=6 recipients, and the data are presented as mean ± SD.

(H) Representative images depicting the immunofluorescence staining of S9.6 in shNT, shRNaseH1 and shRNaseH2A HSPCs using freshly isolated GFP^+ LSK cells from the recipients of (Figure 3I) at the end of the 12^{th} week after transplantation. The panels are shown at the same exposure. The cell nuclei were stained with DAPI.

(I) S9.6 foci distribution in shNT, shRNaseH1 and shRNaseH2A HSPCs.

(J) Representative images depicting the immunofluorescence staining of γH2AX in shNT, shRNaseH1 and RNaseH2A HSPCs using freshly isolated GFP^+ LSK cells from the recipients of (Figure 3I) at the end of the 12^{th} week after transplantation. The panels are shown at the same exposure. The cell nuclei were stained with DAPI.

(K) γH2AX foci distribution in shNT, shRNaseH1 and shRNaseH2A HSPCs.

***Online Supplementary Figure S3*. Aging-increased R-Loop correlates with the lingering RNA in the nucleus of hematopoietic stem cells, related to Figure 3.**

(A) The dot plots show the ratio of nuclear to cytoplasmic Poly(A)$^+$RNA signals in young and aged HSCs. The data are presented as mean ± SD. In the histograms, "N" and "C" represent nuclear and cytoplasmic FISH signals, respectively. N/C ratios were determined for at least 250 cells in each experiment.

(B) This heatmap illustrates the genome-wide subcellular localization of Poly(A)$^+$RNA, represented by normalized Nucleus/Cytoplasm values in aged HSC samples compared to young ones. The color intensity reflects local point density. Spearman's R and p values are indicated. Each dot represents a gene, and the black dashed line represents equality between aged and young HSC samples (X = Y).

(C) This visualization displays the top 10 level-four Biological Process (BP) Gene Ontology (GO) terms significantly enriched with down-expressed genes in aged hematopoietic stem cells (HSCs). The size of each circle corresponds to the amount of overlap between the input gene list and the gene set associated with the GO term. The color of the circle indicates the FDR-adjusted p-value. The x-axis represents the gene ratio of the overlapping gene set to the input gene list.

(D) Enhanced child nodes of the GO term "RNA Localization" with genes exhibiting downregulation in aged HSCs.

(E) The heatmap displays the differential expression levels between aged and young HSCs for genes within the "RNA export from nucleus" GO term across five public RNA-seq datasets. In the heatmap, blue indicates down-regulated genes in aged HSCs, while red indicates up-regulated genes.

(F) The histogram illustrates the relative expression of Alyref in young and aged HSCs. HSCs (CD34$^-$ LSK) , freshly isolated from young (2 months) and aged (24-30 months) mice, are subjected to RT-PCR. The data are presented as mean ± SD.

(G) The western blot image displays the expression of ALYREF in young and aged HSCs. Freshly isolated HSCs (CD34$^-$ LSK) from young (2 months) and aged (24-30 months) mice were subjected to a western blot assay to detect ALYREF.

***Online Supplementary Figure S4*. Targeted dysfunction of Alyref induces R-Loop and disrupts hematopoietic homeostasis, related to Figure 4.**

(**A**) This diagram displays the scheme to generate Alyref$^{flox/flox}$ mice.

(B) Experimental design of Western blot assay for WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ HSPCs. Mx1-Cre^{-}; Alyref$^{flox/flox}$, Mx1-Cre^{+}; Alyref$^{flox/+}$ and Mx1-cre^{+}; Alyref$^{flox/flox}$ mice (abbreviated as WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ in the figure) were treated with Poly I:C every other day for 14 days. Lineage-cells were sorted at 7 days post last Poly I:C injection for Western blot.

(C) Representative Western blot showing the expression of ALYREF in WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ HSPC.

(D-E) Representative fluorescence images depicting the co-localization of R-Loop with γH2AX (D) and RPA (E) in Alyref$^{+/-}$ HSCs.

(F) The dot plot displays the counts of hemoglobin (HGB) and hematocrit (HCT) in WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice. The data are based on at least 7 mice per group and are presented as mean ± SD.

(G) The absolute cell number per femur of WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice was determined based on samples from 6 mice per group.

(H-I) WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice were analyzed for T cells, B cells and myeloid cells. The histogram illustrates the frequency of T cells (CD3^{+}), B cells (B220^{+}) and myeloid cells (CD11b^{+}) in the peripheral blood (H) and bone marrow (I) of WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice. Data from at least 6 mice per group, are presented as mean ± SD.

(J-K) Alyref$^{+/-}$, Alyref$^{-/-}$ and age-matched WT mice, aged 2-3 months were analyzed for hematopoietic stem cells (HSCs) and progenitors. Histograms illustrate the frequency (J) and absolute number (K) of HSC and progenitors in the bone marrow of WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice. Data are based on samples from 6 mice per group.

(L) Illustrated plots demonstrate the gating strategies employed for the analysis of various hematopoietic stem and progenitor cell populations, including LT-HSC (Lineage^{-} Sca1^{+} c-Kit^{+} CD34^{-} CD135^{-}), ST-HSC (Lineage^{-} Sca1^{+} c-Kit^{+} CD34^{+} CD135^{-}), MPP (Lineage^{-} Sca1^{+} cKit^{+} CD34^{+} CD135^{+}), CMP (Lineage^{-} Sca1^{-} c-Kit^{+}

CD16/32^{-} CD34^{+}), GMP (Lineage^{-} Sca1^{-} cKit^{+} CD16/32^{+} CD34^{+}), MEP (Lineage^{-} Sca1^{-} cKit^{+} CD16/32^{+} CD34^{-}), CLP (Lineage^{-} Sca1low c-Kit^{low} CD135^{+} CD127^{+}) cells analysis in the bone marrow of WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ mice.

(M) Experimental design of complete blood count and Poly(A)$^{+}$RNA FISH assay for WT and Alyref$^{+/-}$ mice. Mx1-Cre^{-}; Alyref$^{flox/+}$ and Mx1-Cre^{+}; Alyref$^{flox/+}$ mice (2 months old) were treated with Poly I:C every other day for 14 days. WT and Alyref$^{+/-}$ mice were subjected to complete blood count and Poly(A)$^{+}$RNA FISH assay at 10 months after the last Poly I:C injection.

(N, left illustrative images) Illustrative images displaying the distribution of Poly(A)$^{+}$RNA in both WT and Alyref$^{+/-}$ HSCs are presented. All panels are displayed at identical exposure levels. Detection of Poly(A)$^{+}$RNA utilized a Cy3-labelled oligo(dT)$_{50}$ probe, while nuclei were visualized with DAPI staining.

(N, right dot plot) Dot plots illustrate the ratio of nuclear to cytoplasmic Poly(A)$^{+}$RNA signals in WT and Alyref$^{+/-}$ HSCs. Data are represented as mean ± SD. “N” and “C” denote nuclear and cytoplasmic FISH signals, respectively. N/C ratios were determined for a minimum of 360 cells in each experiment set.

(O) The dot plot displays the quantification of various blood cell types, including white blood cells (WBC), neutrophils (NEUT), lymphocytes (LYM), red blood cells (RBC), basophilic granulocytes (BAS), platelets (PLT), hemoglobin (HGB) and hematocrit (HCT) in both WT and Alyref$^{+/-}$ mice. Each group consists of 13-14 mice, and all data are presented as mean ± SD.

(P) The absolute cell count per femur in both WT and Alyref$^{+/-}$ mice is presented. Each group consists of 6 mice, and the data are expressed as mean ± SD.

(Q-R) Dot plots illustrate the frequency of T cells (CD3^{+}), B cells (B220^{+}) and myeloid cells (CD11b^{+}) in the peripheral blood (Q) and bone morrow (R) of WT and Alyref$^{+/-}$ mice. A minimum of 6 mice per group were analyzed, and all data are presented as mean ± SD.

(S-T) Analysis of HSCs and progenitors was conducted in WT and Alyref$^{+/-}$ mice. Histograms display both the absolute number (S) and frequency (T) of HSCs and progenitors. Each group includes n = 6 mice and the data are presented as mean ± SD.

(U) The experimental design for the competitive transplantation assay involved the use of wild-type (WT), Alyref$^{+/-}$ and Alyref$^{-/-}$ hematopoietic stem cells (HSCs). A total of 100 freshly isolated HSCs were obtained from Mx1-Cre^{-}; Alyref$^{flox/flox}$, Mx1-Cre^{+}; Alyref$^{flox/+}$ and Mx1-Cre^{+}; Alyref$^{flox/flox}$ mice (aged 2-3 months). These HSCs were transplanted into lethally irradiated recipients (CD45.1/2) along with 3×10^5 competitor cells (CD45.1). Peripheral blood (PB) chimerism was assessed 4 weeks post- transplantation. Subsequently, recipients were treated with Poly I:C (12.5 mg/kg) every other day for 14 days. PB chimerism was monitored every 4 weeks up to the 12th week post last Poly I:C injection. Then, freshly isolated 2×10^6 whole bone marrow cells from the primary recipients were transplanted into lethally irradiated recipients (CD45.1/2). The chimerism in the PB of the secondary recipients was examined every 4 weeks until the 12th week.

(V) These line plots show the percentage of donor-derived cells (Overall, B cells, T cells, myeloid cells) in the PB of recipients. n=6-9 recipients per group, data are presented as mean ± SD.

(W) The gating strategy is outlined for assessing the percentage of donor-derived lineage cells (T cells, B cells and myeloid cells) and the lineage distribution of donor-derived T, B and myeloid cells in the peripheral.

(X) The dot plot illustrates the lineage distribution of donor-derived PB cells at the 12th week in secondary recipients. n=6-9 recipients per group, data are presented as mean ± SD.

(Y) A dimensionality reduction plot illustrates WT, Alyref$^{+/-}$ and Alyref$^{-/-}$ HSCs using normalized RNA-seq data of all mouse genes, generated through the PCA (principal component analysis) algorithm.

(Z) These figures present the Gene Set Enrichment Analysis (GSEA) results of cell aging-related genes and HSC fingerprints-related genes in comparisons between WT HSCs vs Alyref$^{-/-}$ HSCs, or WT HSCs vs Alyref$^{+/-}$ HSCs. The normalized enrichment score (NES) and false discovery rate (FDR) q values are provided. A significant difference is indicated by $|NES|>0.3$ and $q<0.05$.

***Online Supplementary Figure S5*. Dysfunction of RNA transportation impairs hematopoietic stem cells, related to Figure 5.**

(A) Representative western blot showing the knockdown efficiency of shRNA against Nxf1 using freshly isolated LSK cells.

***Online Supplementary Figure S6*. Quantitative refill of Alyref rescues the function of aged hematopoietic stem cells by dampening R-Loop and replication stress, related to Figure 6.**

(A) Representative western blot depicting the expression of in Alyref-overexpressed LSK cells. Freshly isolated LSK cells from aged (26 months) mice were infected with Alyref-carrying lentivirus (Alyref OE) and empty vector (EV). After three days, GFP^+ cells were purified for western blot assay with indicated antibodies.

(B) The experimental design of the competitive transplantation assay is described. LSK cells freshly isolated from aged mice (18 months old) were infected with KC and QGES-2^{Alyref} lentivirus, labelled by GFP fluorescence. Three days postinfection, 4000 $GFP^+Sca1^+CD48^-$ cells were purified and transplanted into lethally irradiated recipients (CD45.2) alongside 3×10^5 competitor cells (CD45.1). Chimerism in the peripheral blood was evaluated every 4 weeks until the 16^{th} week. Subsequently, freshly isolated 2×10^6 whole bone marrow cells from the primary recipients were transplanted to lethally irradiated secondary recipients (CD45.2) and chimerism in peripheral blood of the secondary recipients was examined every 4 weeks until the 12^{th} week.

(C-F) Representative images depicting immunofluorescence staining of S9.6 (C) and γH2AX (E) in KC and QGES-2^{Alyref} HSPCs using freshly isolated GFP^+ LSK cells from the primary recipients (*Online Supplementary Figure S6B*) at the end of the 16^{th} week after transplantation. The panels are shown at the same exposure. The cell nuclei were stained with DAPI. (D, F) Distribution of S9.6 (D) and γH2AX (F) foci in KC and QGES-2^{Alyref} HSPCs.

(G) Representative images depicting immunofluorescence staining of RPA in KC and QGES-2^{Alyref} HSPCs. Freshly isolated LSK cells from aged mice (24-30 months) were infected with KC and QGES-2^{Alyref} lentivirus, which is labelled by GFP fluorescence. After three days, GFP^+ cells were purified for immunofluorescence staining. The panels are shown at the same exposure. The cell nuclei were stained with DAPI.

(H) Dot plots depicting the mean fluorescence intensity of RPA in KC and QGES-2^{Alyref} HSPCs. Data are represented as mean ± SD, A minimum of 110 cells

were analyzed in each group.

(I) Representative images depicting the CldU/IdU-labelled DNA replication tracks in KC and QGES-2^{Alyref} HSCs. Freshly isolated HSCs from aged mice (24-30 months) were infected with KC and QGES-2^{Alyref} lentivirus. After three days, GFP^{+} cells were purified for DNA fiber assay.

(J) Dot plots depicting the DNA replication fork symmetry in KC and QGES-2^{Alyref} HSCs. The dot plot of ldU to CIdU track length ratios for individual replication forks. Data are represented as mean ± SD. A minimum of 517 molecules were analyzed in each group.

(K) This chart illustrates the proposed model of Alyref→RNA exportation→R-Loop→DNA replication stress promotes hematopoietic stem cell aging.

O*nline Supplementary Table S1.* Geneotyping primer

O*nline Supplementary Table S2.* shRNA and clone primer

O*nline Supplementary Table S3.* Flow cytometric analysis and cell sorting antibody

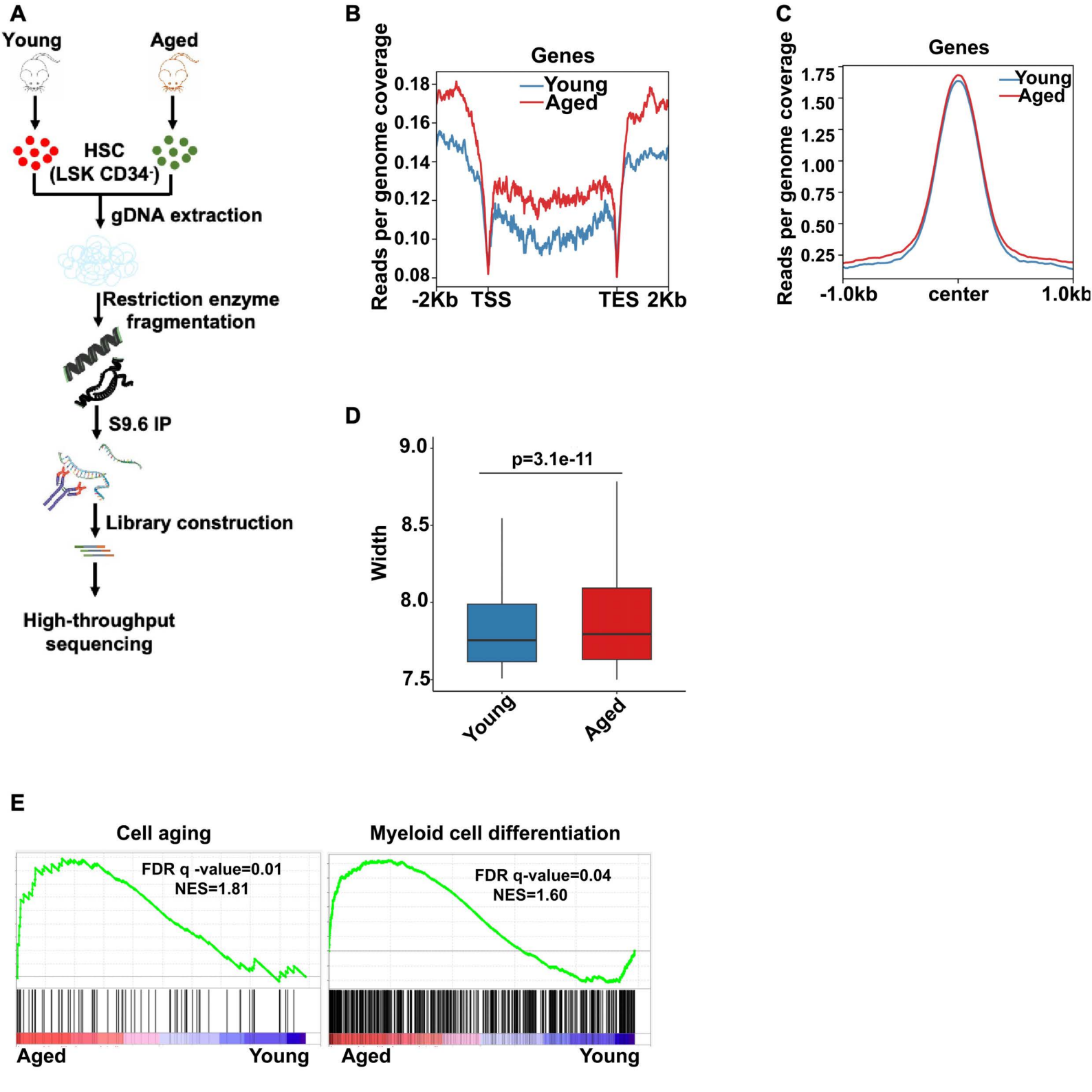
O*nline Supplementary Table S4.* Western blot and Immunofluorescence staining antibody

O*nline Supplementary Table S5.* RT-PCR primer list

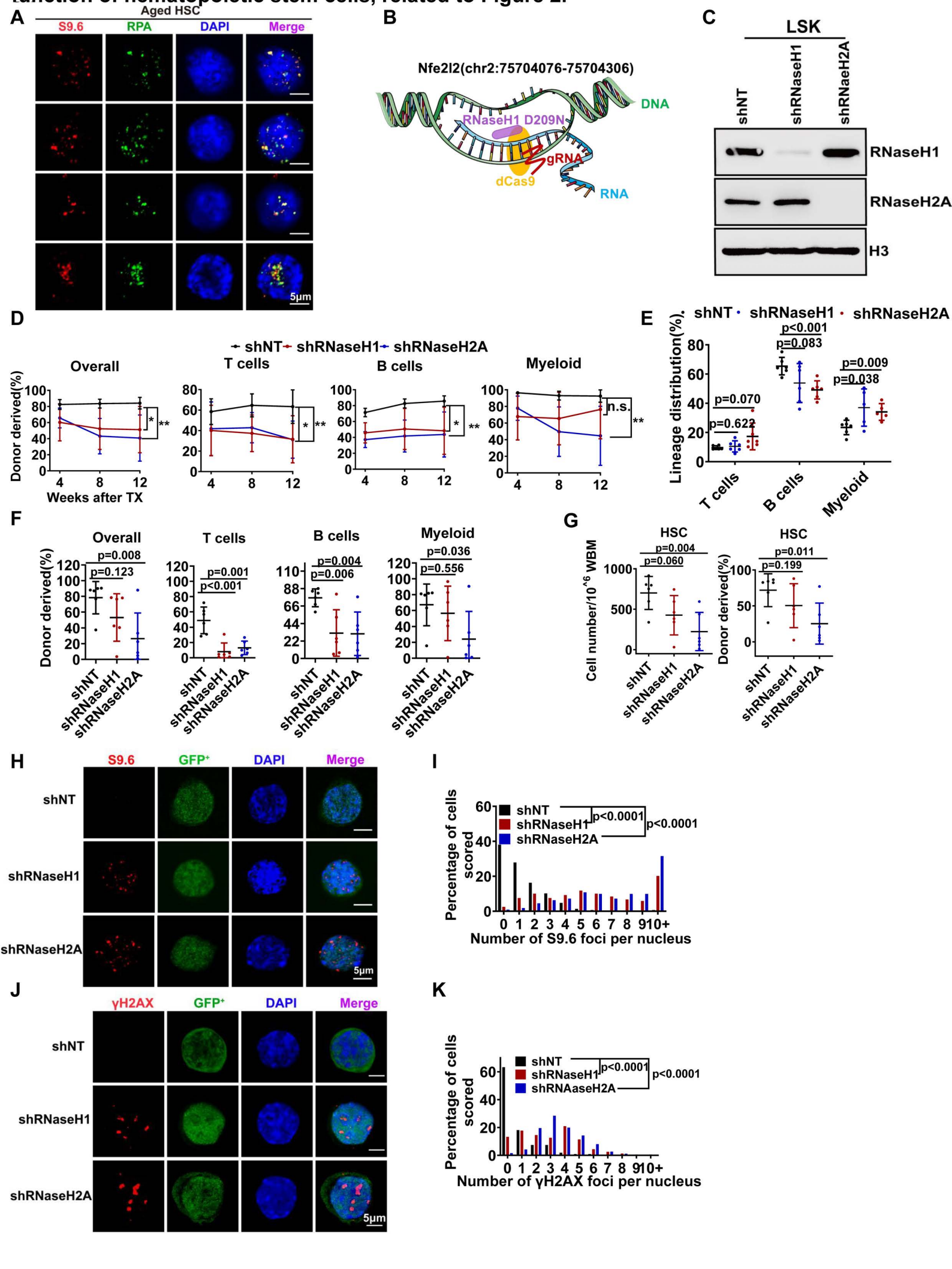
O*nline Supplementary Table S6.* gRNA primer

O*nline Supplementary Table S7.* HSC figerprint gene, Cell aging and Myeloid cell differentiation

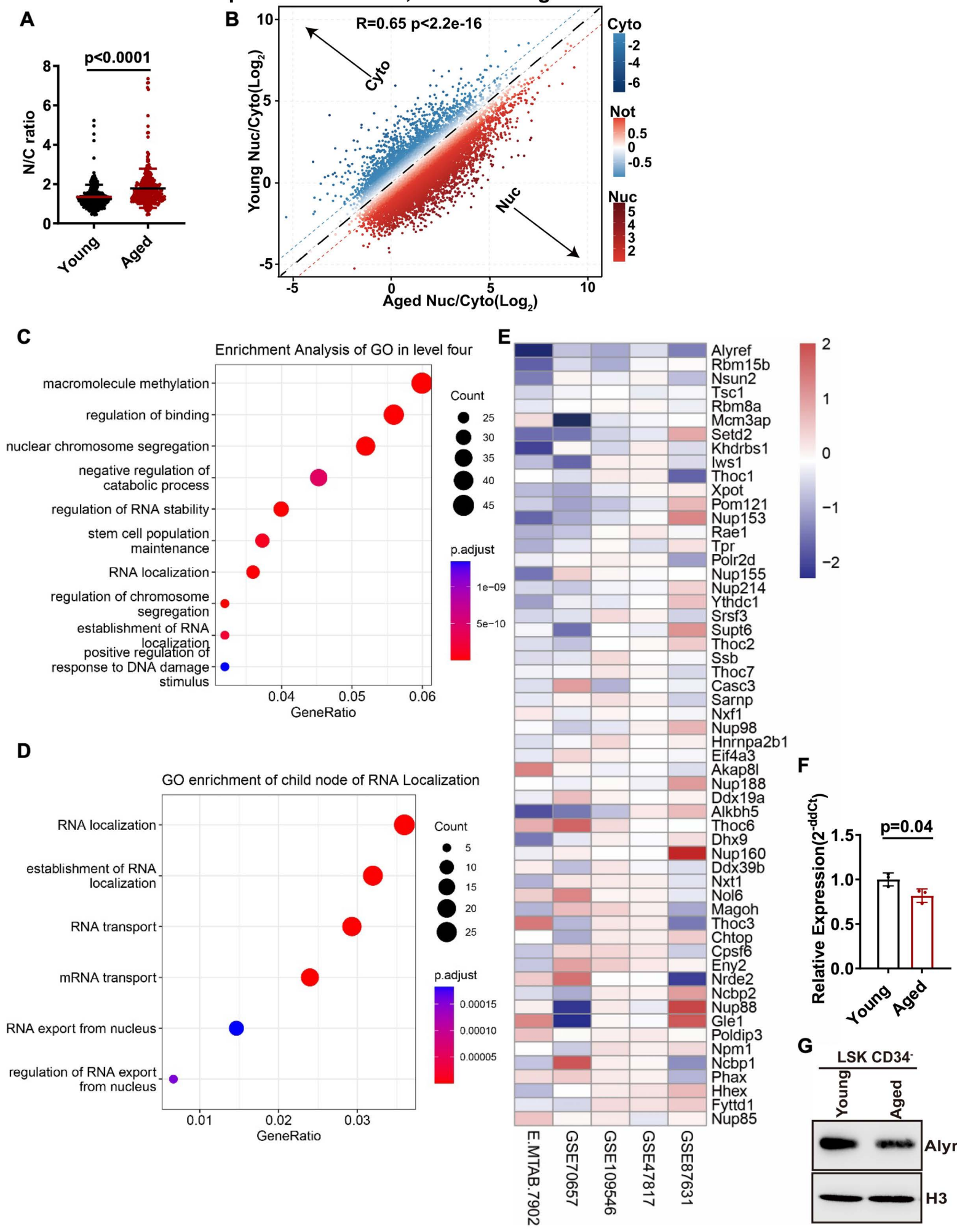
***Online Supplementary Figure S1*. R-Loop is increased in aged hematopoietic stem cells, related to Figure 1.**



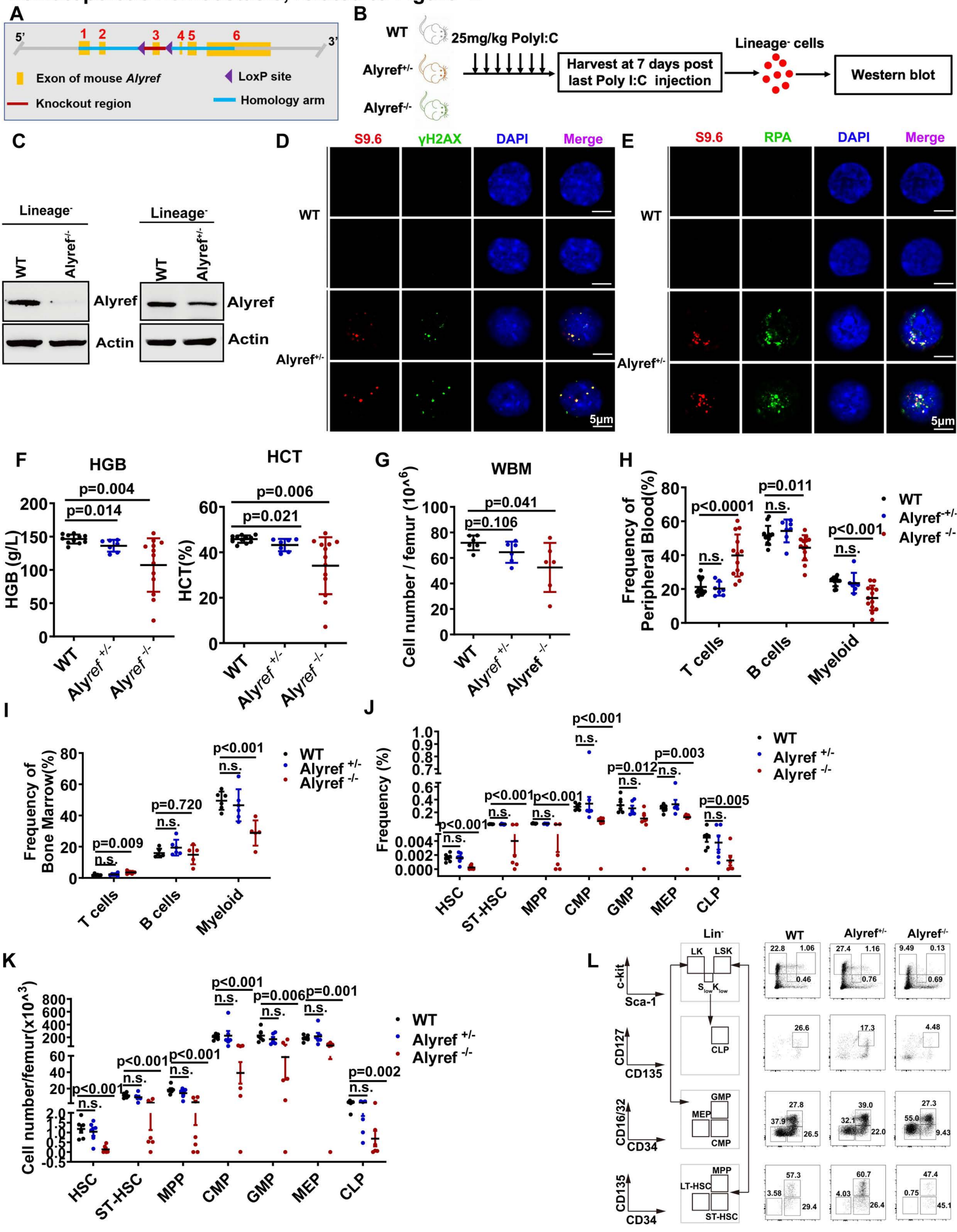
Online Supplementary Figure S2. **Accumulated R-Loop induces DNA damage and impairs the function of hematopoietic stem cells, related to Figure 2.**



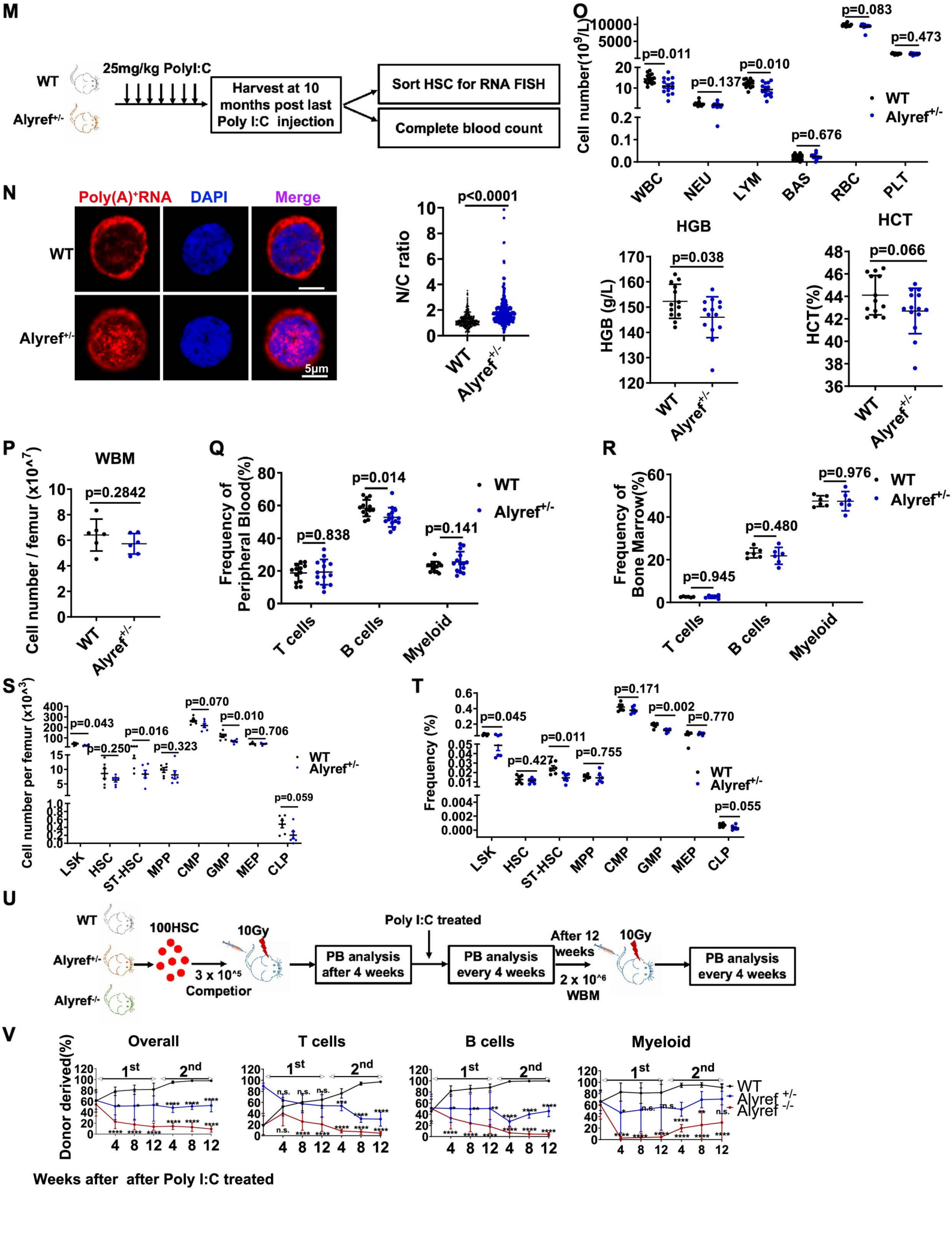
***Online Supplementary Figure S3*. Aging-increased R-Loop correlates with the lingering RNA in the nucleus of hematopoietic stem cells, related to Figure 3.**



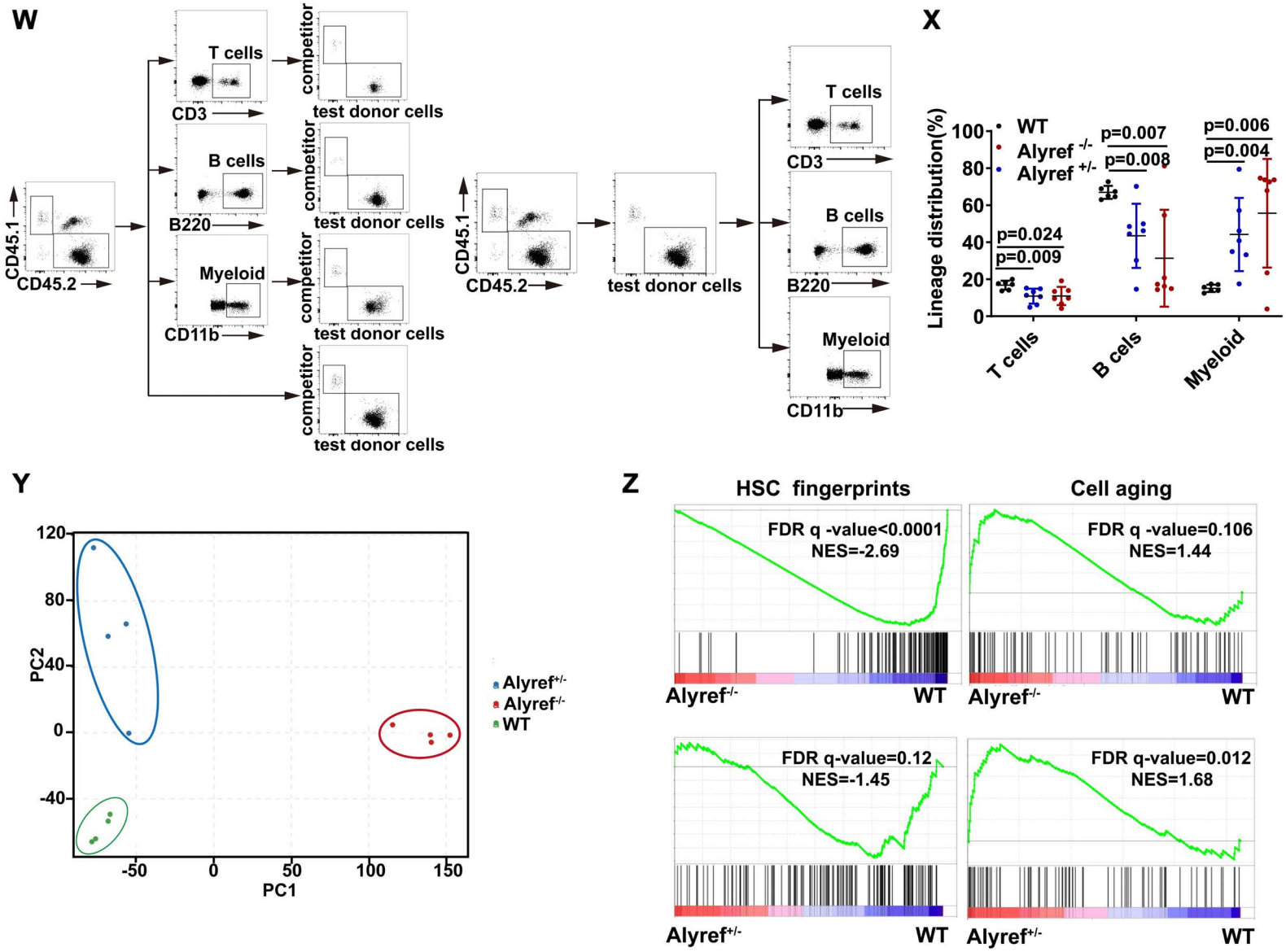
***Online Supplementary Figure S4*. Targeted dysfunction of Alyref induces R-Loop and disrupts hematopoietic homeostasis, related to Figure 4.**



***Online Supplementary Figure S4*. Targeted dysfunction of Alyref induces R-Loop and disrupts hematopoietic homeostasis, related to Figure 4.**

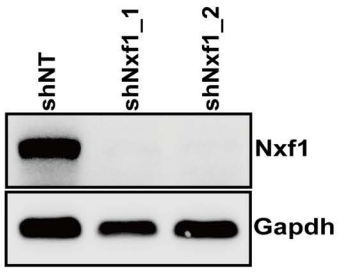


***Online Supplementary Figure S4*. Targeted dysfunction of Alyref induces R-Loop and disrupts hematopoietic homeostasis, related to Figure 4.**

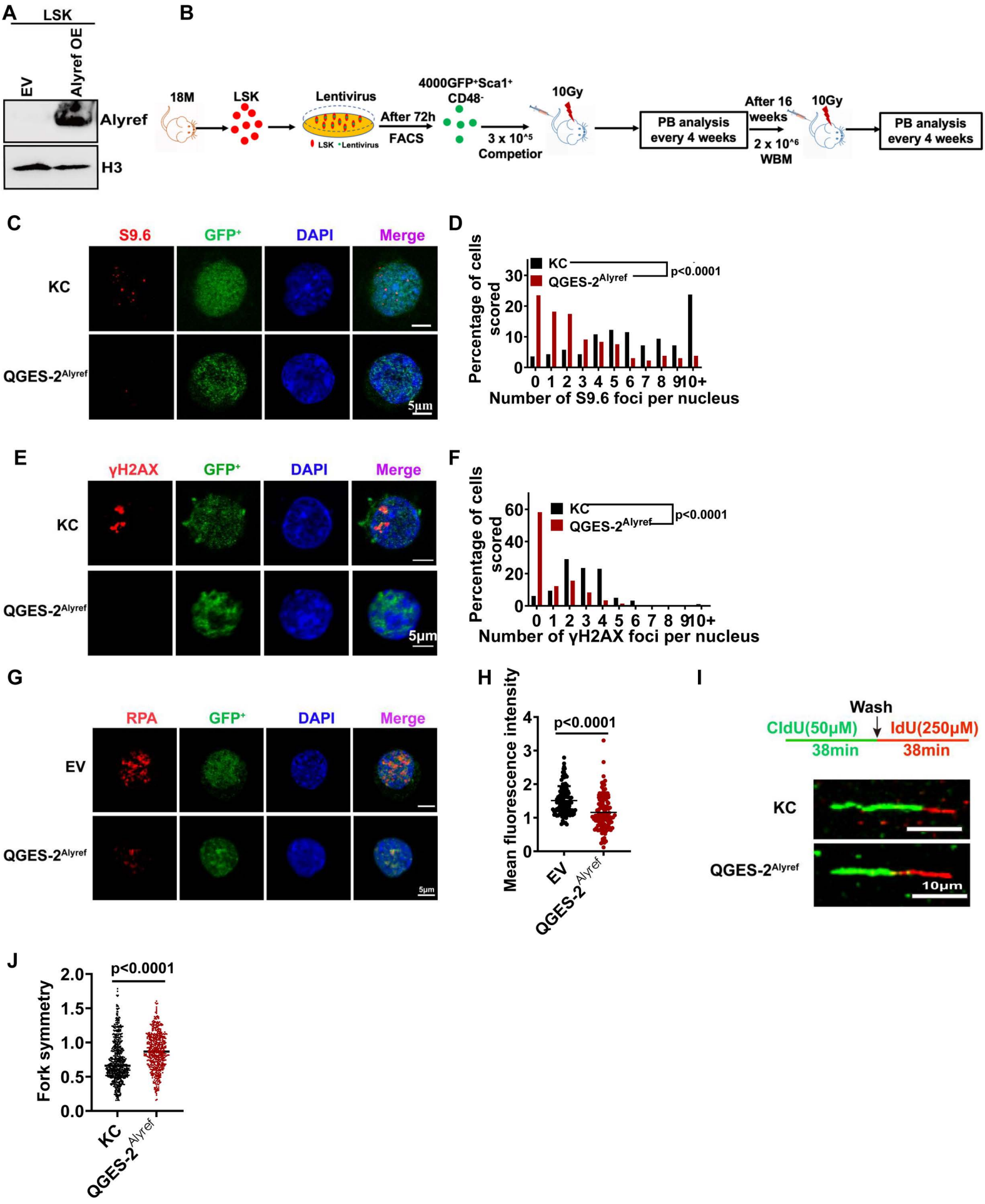


***Online Supplementary Figure S5*. Dysfunction of RNA transportation impairs hematopoietic stem cells, related to Figure 5.**

A

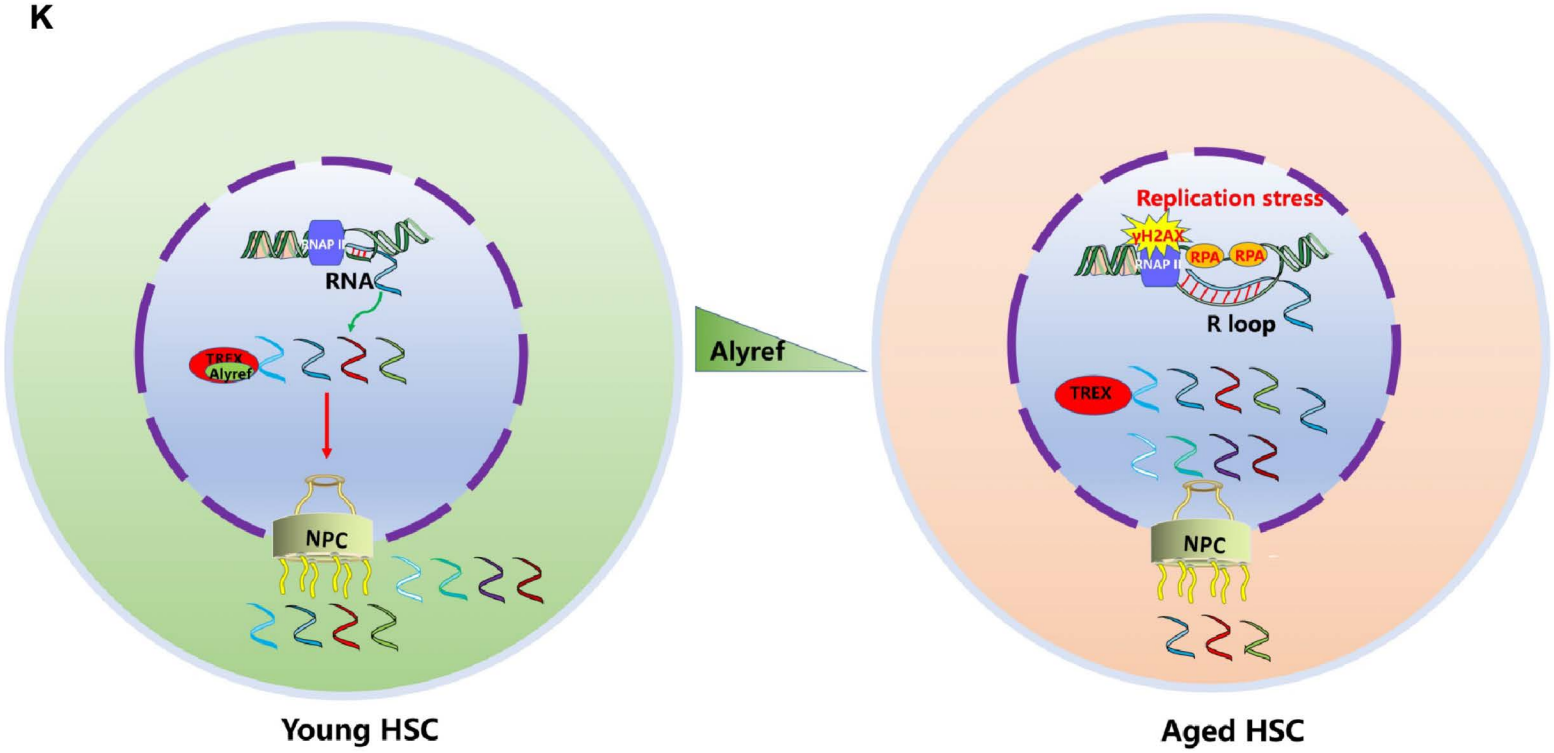


***Online Supplementary Figure S6*. Quantitative refill of Alyref rescues the function of aged hematopoietic stem cells by dampening R-Loop and replication stress, related to Figure 6.**



***Online Supplementary Figure S6*. Quantitative refill of Alyref rescues the function of aged hematopoietic stem cells by dampening R-Loop and replication stress, related to Figure 6.**

K



***Online Supplementary Table S1*. Geneotyping primer**

	Forward (5'-3')	Reverse(5'-3')
Alyref$^{f/f}$	ATTTCACTTCAGACTTGGCAGCAG	CCAGAGGCCAATAGTAAAACTGTC
Mx1-cre	GCGGTCTGGCAGTAAAAACTATC（F1）	GTGAAACAGCATTGCTGTCACTT（R1）
	CTAGGCCACAGAATTGAAAGATCT（F2）	GTAGGTGGAAATTCTAGCATCATCC（R2）

***Online Supplementary Table S2*. shRNA and clone primer**

Gene	Sequence
Thoc1	ACAGATTGAGTGTGACAGTGAA
Thoc5	ATGGCAGAGACTATGAGTTGTA
Nxf1_1	AAAGGATATCTATCATCATCAA
Nxf1_2	CCGCGAACGATTTCCCAAGTTA
RNaseH1	AAGACAGCATGTTCACCATCAA
RNaseH2A	ACCAGGAATAAAAGCTGTTCAA
shRNA clone primer	ACTTCGACTTCTTAACCCAACAGAAGGCTCGAGAAGGTATATTGCTGTTGACAGTGAGCG (Forward, 5'-3')
	GTTTTAGTAAACAAGATAATTGCTCGAATTCTAGCCCCTTGAAGTCCGAGGCAGTAGGCA (Reverse, 5'-3')

***Online Supplementary Table S3*. Flow cytometric analysis and cell sorting antibody**

Name	Manufacturer	Cat#	RRID	Clone
Biotin B220 anti-mouse	Biolegend	103204	AB_312989	RA3-6B2
Biotin Ly-6G and Ly-6C anti-mouse	Biolegend	108404	AB_313369	RB6-8C5
Biotin CD8a anti-mouse	Biolegend	100704	AB_312743	53-6.7
Biotin CD3ε anti-mouse	Biolegend	100304	AB_312669	145-2C11
Biotin CD4 anti-mouse	Biolegend	100508	AB_312711	RM4-5
Biotin CD11b anti-mouse	Biolegend	101204	AB_312787	M1/70
Biotin Ter-119 anti-mouse	Biolegend	116204	AB_313705	TER-119
FITC CD45.2 anti-mouse	Biolegend	109806	AB_313443	104
Pacific Blue™ B220 anti-mouse	Biolegend	103227	AB_492876	RA3-6B2
APC CD3ε anti-mouse	Biolegend	100312	AB_312677	145-2C11
PerCP-Cy™5.5 CD11b anti-mouse	Biolegend	101228	AB_893232	M1/70
Alexa Fluor® 700 Gr1 anti-mouse	Biolegend	108422	AB_2137487	RB6-8C5
PE CD45.1 anti-mouse	Biolegend	110708	AB_313497	A20
FITC CD8a anti-mouse	Biolegend	100706	AB_312745	53-6.7
PE CD4 anti-mouse	Biolegend	100512	AB_312715	RM4-5
Streptavidin APC-efluor780	Invitrogen	47-4317-82	AB_10366688	
PerCP/Cyanine5.5 CD127 anti-mouse	Biolegend	135022	AB_1937273	A7R34
PE CD150 anti-mouse	Biolegend	115904	AB_313683	TC15-12F12.2
APC CD117 anti-mouse	Invitrogen	17-1171-83	AB_469431	2B8

Online Supplementary Table S3 **(Continued).**

Name	Manufacturer	Cat#	RRID	Clone
PE/Cyanine7 CD150 anti-mouse	Biolegend	115914	AB_439797	TC15-12F12.2
PE/Cyanine7 CD16/32 anti-mouse	Biolegend	101318	AB_2104156	93
PE-Cy™7 Sca-1 anti-mouse	Invitrogen	25-5981-82	AB_469669	D7
BV421 CD127 anti-mouse	Biolegend	135024	AB_11218800	A7R34
FITC CD16/CD32 anti-mouse	Biolegend	101306	AB_312805	93
PE-CF594 CD135 anti-mouse	BD Biosciences	562537	AB_2737639	A2F10.1
FITC CD34 anti-mouse	Invitrogen	11-0341-85	AB_465022	RAM34
Alexa Fluor® 700 CD34 anti-mouse	Invitrogen	56-0341-82	AB_493998	RAM34

***Online Supplementary Table S4*. Western blot and Immunofluorescence staining antibody**

Name	Manufacturer	Cat#	RRID	Clone
Rabbit anti-Histone H3	Cell Signaling Technology	4499	AB_10544537	D1H2
Rabbit anti-β-Actin	Cell Signaling Technology	4970	AB_2223172	
Rabbit anti-Gapdh	Abclonal	AC001	AB_2619673	
Rabbit Anti-Mouse IgG (HRP Conjugate)	Cell Signaling Technology	58802	AB_2799549	D3V2A
Mouse Anti-Rabbit IgG (HRP Conjugate)	Cell Signaling Technology	93702	AB_2800208	D4W3E
Anti-Mouse IgG Alexa Fluor® 594	Invitrogen	A-11005	AB _2534073	
Anti-Rabbit IgG Alexa Fluor® 488	Invitrogen	A-11008	AB _143165	
Anti-Rat IgG Alexa Fluor® 488	Invitrogen	A-11006	AB _2534074	
Anti-Rabbit IgG Alexa Fluor® 647	Invitrogen	A-21245		
Anti-Mouse IgG Alexa Fluor® 647	Abcam	ab150115		
Mouse -γH2AX	Millipore	05-636		
Rabbit -Nxf1	Abclonal	A5907		
Rat anti-RPA	Cell Signaling Technology	2208s		
Rabbit -RNaseH1	Abclonal	A9116		

Online Supplementary Table S4 **(Continued).**

Name	Manufacturer	Cat#	RRID	Clone
Rabbit -RNaseH2A	Abclonal	A15132		
Rat anti-CIdU	Abcam	ab6326		
Mouse anti-IdU	Becton Dickinson	347580		
Mouse anti-S9.6	Millipore	MABE1095		
Rabbit -Alyref	Abcam	ab202894		
Rabbit -Alyref	Cell Signaling Technology	12655		
Rabbit -γH2AX	Cell Signaling Technology	9718		

***Online Supplementary Table S5*. RT-PCR primer list**

Gene	Forward(5'-3')	Reverse(5'-3')
Actin	GTGACGTTGACATCCGTAAAGA	GCCGGACTCATCGTACTCC
Alyref	ACCGAAACAACTTCCCGACAA	CACATCTGCTGTCCCTAAACTT
Thoc1	GTGACCGAAAGTGTTTGTACTGC	CTGAGGAGATCATTGCACATACG
Thoc5	GGACCTGAAGAGTAAGGGCAG	CTGATGTGGGCTAATCGGTTAAG

Online Supplementary Table S6. **gRNA primer**

Gene	Sequence
Nfe2l2	CTGCGCCTCCCACCCAGC
	TTGCCCTCCCAGCTCGGC
ssDRIP-qPCR primer	
Forward(5'-3')	GCGAGGTGGTGGTGTCTC
Reverse(5'-3')	AACGGAGGATGTTGGGGC

Online Supplementary Table S7.

HSC figerprint gene

Column1	Column2
ENSMUSG00000073293	Nudt10
ENSMUSG00000071723	Gspt2
ENSMUSG00000070822	Zscan18
ENSMUSG00000068270	Shroom4
ENSMUSG00000062098	Btbd3
ENSMUSG00000061762	Tac1
ENSMUSG00000058135	Gstm1
ENSMUSG00000057614	Gnai1
ENSMUSG00000056758	Hmga2
ENSMUSG00000055799	Tcf7l1
ENSMUSG00000055737	Ghr
ENSMUSG00000055692	Tmem191
ENSMUSG00000054252	Fgfr3
ENSMUSG00000053080	Zfta
ENSMUSG00000052155	Acvr2a
ENSMUSG00000050953	Gja1
ENSMUSG00000049791	Fzd4
ENSMUSG00000049536	Tceal1
ENSMUSG00000049382	Krt8
ENSMUSG00000048960	Prex2
ENSMUSG00000048537	Phldb1
ENSMUSG00000048489	Depp1
ENSMUSG00000048388	Fam171b
ENSMUSG00000046402	Rbp1
ENSMUSG00000045954	Cavin2
ENSMUSG00000045103	Dmd
ENSMUSG00000044393	Dsg2
ENSMUSG00000043518	Rai2
ENSMUSG00000042826	Fgf11
ENSMUSG00000042340	Ctf1
ENSMUSG00000040891	Foxa3
ENSMUSG00000040537	Adam22
ENSMUSG00000040289	Hey1
ENSMUSG00000039943	Plcb4
ENSMUSG00000039765	Cc2d2a
ENSMUSG00000039084	Chad
ENSMUSG00000038700	Hoxb5

ENSMUSG00000038235	F11r
ENSMUSG00000037440	Vnn1
ENSMUSG00000037169	Mycn
ENSMUSG00000036564	Ndrg4
ENSMUSG00000036356	Csgalnact1
ENSMUSG00000036120	Rfxank
ENSMUSG00000035413	Tmem98
ENSMUSG00000034795	Ccdc122
ENSMUSG00000034771	Tle2
ENSMUSG00000034382	AI661453
ENSMUSG00000034037	Fgd5
ENSMUSG00000033590	Myo5c
ENSMUSG00000033585	Ndn
ENSMUSG00000033032	Afap1l1
ENSMUSG00000032968	Inha
ENSMUSG00000032717	Mdfi
ENSMUSG00000032547	Ryk
ENSMUSG00000032348	Gsta4
ENSMUSG00000032194	Kank2
ENSMUSG00000031997	Trpc6
ENSMUSG00000031870	Pgr
ENSMUSG00000031778	Cx3cl1
ENSMUSG00000031740	Mmp2
ENSMUSG00000031548	Sfrp1
ENSMUSG00000031503	Col4a2
ENSMUSG00000031502	Col4a1
ENSMUSG00000031375	Bgn
ENSMUSG00000031290	Lrch2
ENSMUSG00000030796	Tead2
ENSMUSG00000030711	Sult1a1
ENSMUSG00000030208	Emp1
ENSMUSG00000030088	Aldh1l1
ENSMUSG00000030022	Adamts9
ENSMUSG00000029661	Col1a2
ENSMUSG00000029469	Ift81
ENSMUSG00000029311	Hsd17b11
ENSMUSG00000029267	Mtf2
ENSMUSG00000028957	Per3
ENSMUSG00000028469	Npr2
ENSMUSG00000028463	Car9

ENSMUSG00000028402	Mpdz
ENSMUSG00000028023	Pitx2
ENSMUSG00000027954	Efna1
ENSMUSG00000027800	Tm4sf1
ENSMUSG00000027684	Mecom
ENSMUSG00000027669	Gnb4
ENSMUSG00000027661	Slc2a10
ENSMUSG00000027646	Src
ENSMUSG00000027559	Car3
ENSMUSG00000027499	Pkia
ENSMUSG00000027358	Bmp2
ENSMUSG00000027351	Spred1
ENSMUSG00000026994	Galnt3
ENSMUSG00000026826	Nr4a2
ENSMUSG00000026814	Eng
ENSMUSG00000026796	Niban2
ENSMUSG00000026604	Ptpn14
ENSMUSG00000026436	Elk4
ENSMUSG00000026315	Serpinb8
ENSMUSG00000025887	Casp12
ENSMUSG00000025584	Pde8a
ENSMUSG00000025094	Slc18a2
ENSMUSG00000024940	Ltbp3
ENSMUSG00000024924	Vldlr
ENSMUSG00000024486	Hbegf
ENSMUSG00000024420	Zfp521
ENSMUSG00000024268	Celf4
ENSMUSG00000024109	Nrxn1
ENSMUSG00000023828	Slc22a3
ENSMUSG00000023092	Fhl1
ENSMUSG00000023043	Krt18
ENSMUSG00000022995	Enah
ENSMUSG00000022941	Ripply3
ENSMUSG00000022479	Vdr
ENSMUSG00000022297	Fzd6
ENSMUSG00000021379	Id4
ENSMUSG00000021268	Meg3
ENSMUSG00000020773	Trim47
ENSMUSG00000020635	Fkbp1b
ENSMUSG00000020364	Zfp354a

ENSMUSG00000020176	Grb10
ENSMUSG00000019894	Slc6a15
ENSMUSG00000019768	Esr1
ENSMUSG00000018845	Unc45b
ENSMUSG00000018800	Abca5
ENSMUSG00000017390	Aldoc
ENSMUSG00000016494	Cd34
ENSMUSG00000015053	Gata2
ENSMUSG00000014932	Yes1
ENSMUSG00000014704	Hoxa2
ENSMUSG00000009378	Slc16a12
ENSMUSG00000008305	Tle1
ENSMUSG00000007989	Fzd3
ENSMUSG00000006389	Mpl
ENSMUSG00000006386	Tek
ENSMUSG00000004267	Eno2
ENSMUSG00000004044	Cavin1
ENSMUSG00000003949	Hlf
ENSMUSG00000003226	Ranbp2
ENSMUSG00000002799	Jag2
ENSMUSG00000002265	Peg3
ENSMUSG00000000938	Hoxa10
ENSMUSG00000000753	Serpinf1
ENSMUSG00000000058	Cav2
ENSMUSG00000000031	H19

Cell aging

Column1	Column2
ENSEMBL	SYMBOL
ENSMUSG00000030562	Nox4
ENSMUSG00000025499	Hras
ENSMUSG00000001517	Foxm1
ENSMUSG00000020364	Zfp354a
ENSMUSG00000054580	Pla2r1
ENSMUSG00000055917	Zfp277
ENSMUSG00000022982	Sod1
ENSMUSG00000023067	Cdkn1a
ENSMUSG00000027820	Mme
ENSMUSG00000024975	Pdcd4

ENSMUSG00000040274	Cdk6
ENSMUSG00000063049	Ing2
ENSMUSG00000028063	Lmna
ENSMUSG00000000093	Tbx2
ENSMUSG00000022510	Trp63
ENSMUSG00000022508	Bcl6
ENSMUSG00000041577	Prelp
ENSMUSG00000020032	Nuak1
ENSMUSG00000020608	Smc6
ENSMUSG00000003190	Bcl2l12
ENSMUSG00000052056	Zfp217
ENSMUSG00000029454	Mapkapk5
ENSMUSG00000021918	Nek4
ENSMUSG00000001707	Eef1e1
ENSMUSG00000018604	Tbx3
ENSMUSG00000031583	Wrn
ENSMUSG00000067847	Romo1
ENSMUSG00000019942	Cdk1
ENSMUSG00000031540	Kat6a
ENSMUSG00000029521	Chek2
ENSMUSG00000020235	Fzr1
ENSMUSG00000039456	Morc3
ENSMUSG00000003549	Ercc1
ENSMUSG00000041147	Brca2
ENSMUSG00000049300	Prmt6
ENSMUSG00000003814	Calr
ENSMUSG00000005846	Rsl1d1
ENSMUSG00000059552	Trp53
ENSMUSG00000030265	Kras
ENSMUSG00000057113	Npm1
ENSMUSG00000021948	Prkcd
ENSMUSG00000033307	Mif
ENSMUSG00000021611	Tert
ENSMUSG00000053436	Mapk14
ENSMUSG00000007817	Zmiz1
ENSMUSG00000020644	Id2
ENSMUSG00000042675	Ypel3
ENSMUSG00000059586	Nsmce2
ENSMUSG00000049932	H2ax
ENSMUSG00000026842	Abl1

ENSMUSG00000020063	Sirt1
ENSMUSG00000078249	Hmga1b
ENSMUSG00000013663	Pten
ENSMUSG00000031921	Terf2
ENSMUSG00000000282	Mnt
ENSMUSG00000036986	Pml
ENSMUSG00000015605	Srf
ENSMUSG00000020464	Pnpt1
ENSMUSG00000024943	Smc5
ENSMUSG00000057329	Bcl2
ENSMUSG00000004069	Dnaja3
ENSMUSG00000023307	Marchf5
ENSMUSG00000038084	Opa1
ENSMUSG00000024174	Pot1b
ENSMUSG00000021256	Vash1
ENSMUSG00000022672	Prkdc
ENSMUSG00000037405	Icam1
ENSMUSG00000034218	Atm
ENSMUSG00000046711	Hmga1
ENSMUSG00000055116	Arntl
ENSMUSG00000035799	Twist1
ENSMUSG00000030890	Ilk
ENSMUSG00000056758	Hmga2
ENSMUSG00000028991	Mtor
ENSMUSG00000026814	Eng
ENSMUSG00000004936	Map2k1
ENSMUSG00000020898	Ctc1
ENSMUSG00000035873	Pawr
ENSMUSG00000021796	Bmpr1a

Myeloid cell differentiation

Column1	Column2
ENSEMBL	SYMBOL
ENSMUSG00000066677	Ifi208
ENSMUSG00000035692	Isg15
ENSMUSG00000074417	Pira11
ENSMUSG00000074417	Pira6
ENSMUSG00000074417	Pira7
ENSMUSG00000074417	Pira12
ENSMUSG00000090272	Mndal

ENSMUSG00000074419	Pira6
ENSMUSG00000074419	Pira13
ENSMUSG00000095675	Ccl21b
ENSMUSG00000079108	Srp54c
ENSMUSG00000043252	Tmem64
ENSMUSG00000043510	Hscb
ENSMUSG00000093938	Evi2b
ENSMUSG00000118991	Mir451b
ENSMUSG00000037849	Ifi206
ENSMUSG00000039461	Tcta
ENSMUSG00000021901	Bap1
ENSMUSG00000002326	Gmpr2
ENSMUSG00000022488	Nckap1l
ENSMUSG00000073414	Mpig6b
ENSMUSG00000024958	Gpr137
ENSMUSG00000053799	Exoc6
ENSMUSG00000049086	Bmyc
ENSMUSG00000056962	Jmjd6
ENSMUSG00000034274	Thoc5
ENSMUSG00000030067	Foxp1
ENSMUSG00000015143	Actn1
ENSMUSG00000024026	Glo1
ENSMUSG00000069917	Hba-a2
ENSMUSG00000052435	Cebpe
ENSMUSG00000058835	Abi1
ENSMUSG00000022878	Adipoq
ENSMUSG00000000532	Acvr1b
ENSMUSG00000052155	Acvr2a
ENSMUSG00000025473	Adam8
ENSMUSG00000029106	Add1
ENSMUSG00000032786	Alas1
ENSMUSG00000025270	Alas2
ENSMUSG00000032041	Tirap
ENSMUSG00000031543	Ank1
ENSMUSG00000016319	Slc25a5
ENSMUSG00000024997	Prdx3
ENSMUSG00000021686	Ap3b1
ENSMUSG00000005871	Apc
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