Supplemental Information

miR-15a/16-1 deletion in activated B-cells promotes plasma cell and mature B-cell neoplasms

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Supplemental Methods

miR ISH, and IF/ISH double stains

For ISH, rehydrated slides were incubated with HCl (0.2M, RT, 20min), treated with proteinase K (100µg/ml, 37°C, 20min; Invitrogen), re-fixed with paraformaldehyde (PFA; 4% in PBS, RT, 5min), with each step followed by washing, and air-dried. Digoxigenin (DIG)-labeled locked-nucleic acid (LNA) probes (**supplemental Table 2**; Bio Basic) were hybridized in DIG Easy Hyb buffer (Roche) for 18h at 4°C, washed, blocked, and developed with anti-DIG-AP (Roche) and a solution of nitro blue tetrazolium chloride and 5-bromo-4-chloro-3-indolyl-phosphate (NBT/BCIP; Roche). The slides were counterstained with Fast Red (Sigma) or mounted without counterstaining. Expression of miR-15a and miR-16 was checked across mouse tissues using RT-qPCR and ISH, and muscle and thymus were used as negative and positive parallel controls, respectively (**supplemental Figure 8A-B**). Tissues from *WT* and *KO* mice were placed on a single paraffin block and processed in parallel. Control and malignant human tissues were likewise processed at the same time.

For miR-15a/16/CD138 IF/ISH double-staining, frozen human LN sections were fixed with 4% PFA for 30 min, washed, blocked with 5% BSA for 20 min, and stained with primary anti-CD138 antibody (#MCA2459GA, Bio-Rad Laboratories) for 18h at 4°C, then with secondary anti-mouse IgG Alexa Flour 488 conjugate (#A-11029, Invitrogen) for 2h at room temperature. Sections were counterstained with 4',6-diamidino-2-phenylindole (DAPI; Sigma), mounted using BrightMount medium (Abcam), and scanned in IF mode. Thereafter, coverslips were removed and sections were re-fixed in 10% formalin for 10 min, dried, baked, rehydrated, and processed according to the ISH protocol described above but without the counterstaining. Slides were next scanned in the bright-field mode.

Given better epitope preservation, miR-16/CD10 and miR-16/PD-1 ISH/IHC double-staining was performed on FFPE sections according to standard ISH protocol, followed by standard IHC protocol and development with PermaRed/AP.

IF, IHC, and ISH image acquisition and analyses

IHC and ISH images were acquired using Leica DM2000 microscope (Leica Microsystems) unless otherwise specified. Ki-67, cleaved caspase-3, CD138, and VEGF-A stainings in spleens of immunized *WT* and *KO* mice were scanned using Vectra 2 Intelligent Slide Analysis System (Caliper LifeSciences). Intensity of pERK staining, area of GCs, and percentage of $CD138^+$ PCs were assessed using HALO Image Analysis Software (PerkinElmer). GC area was normalized to the total tissue area. Percentage of cells positive for cleaved caspase-3 was assessed using inForm Cell Analysis software (PerkinElmer).

For IF/ISH and IHC/ISH double stains, slides were scanned using the Vectra 2 Intelligent Slide Analysis System. IF/ISH binary images were overlaid according to slide coordinates using Photoshop (Adobe). Red was employed for miR ISH, green for CD138 IF, and blue for DAPI IF channels in both individual and merged images. For miR-15a, miR-16, and CD138 IHC colocalization, serial consecutive sections were scanned using ScanScope slide scanner (Aperio).

EP cases (n=11) were scored into three categories ‘strong’, ‘week’, and ‘negative’ as compared to normal nodal PCs independently by two certified pathologists.

Immunoglobin heavy chain (*IgH*) variable region mutation analysis

IgH variable regions were amplified from genomic DNA by PCR using Phusion High-Fidelity PCR Master Mix (New England Biolabs) and appropriate primers (**supplemental Table 2**). Clonal bands were extracted from agarose (Sigma) gels with a QIAquick Gel Extraction Kit (Qiagen) and cloned with a Zero Blunt TOPO PCR Cloning Kit (Invitrogen). Plasmids were prepared using a QIAprep Spin Miniprep Kit (Qiagen), sequenced, and analyzed using the international ImMunoGeneTics information system.[1]

Whole-exome sequencing

For mouse analysis WES was performed on one EP and one DLBCL FFPE samples as well as one FFPE spleen from a healthy animal as a control as described;[2] except, 200ng of DNA was used for libraries preparation and sequenced on NovaSeq 6000 (Illumina). Mean target coverage was 123X. Reads were processed and analyzed as described.[2] Mutations were compared to human lymphoid malignancies from cBioPortal and mapped on proteins with maftools.[3-17]

Human WES was performed on eleven FFPE samples from primary EP cases and one control. Libraries were prepared using KAPA HyperPrep Kit (Roche). Sequencing libraries were constructed using SureSelect Human All Exon V5 plus POPv3.1 SV ONLY 3191451 spike-in and SureSelect XT HS Hybrid Capture kit (Agilent), pooled and sequenced using NovaSeq 6000 (Illumina). Mean target coverage was 152X (range 107-212X). Paired-end reads were aligned to the reference human genome using BWA-mem.[18] Duplicated reads were marked and base quality score recalibration was performed using MarkDuplicates and ApplyBQSR with GATK4.[19,20] Mutect2 was used to call single nucleotide variants (SNVs) and small insertions and deletions (indels). Raw mutation calls then filtered using FilterMutectCalls from GATK4 and only the mutations PASS all the filters applied by FilterMutectCalls and has at least 10X coverage for tumor samples extracted with bcftools for further analysis. SNVs and indels were annotated using Variant Effect Predictor (VEP) from Ensembl and converted to MAF files using VCF2MAF.[21,22] dbSNP v154 were used filter SNP sites and the population variant resource containing allele-specific frequencies from gnomAD to filter alleles.[23,24] COSMIC and cBioPortal databases were used to identify somatic mutations.[4,25,26] Chromosome arm level copy number variants were identified using RobustCNV, which relies on localized changes in the mapping depth of sequenced reads to identify changes in copy number at the loci sampled during targeted capture. Mutation calls were validated using Sanger sequencing. Single nucleotide and copy number variants were compared to MM and visualized using maftools and R.[3,27-30] Pathways were assigned using OncogenicPathways function.[3] Chromosomal rearrangements were visualized

using Circos and ClicO FS.[31,32] Genetic alterations were clustered using 1-pearson correlation and visualized using Morpheus (https://software.broadinstitute.org/morpheus).

Amplicon sequencing

Gna13, *Hist1h1c*, *Hist1h1e*, and *Pim1* coding regions were amplified from genomic DNA (*Hist1h1c* and *Hist1h1e*) or cDNA (*Gna13* and *Pim1*) using Q5 DNA Polymerase (New England Biolabs) and purified using QIAquick Gel Extraction Kit (Qiagen). Amplicons were fragmented to approximately 250bp using Covaris adaptive focused acoustics on the M220 platform. Illumina sequencing libraries were prepared using Swift S2 Acel reagents on a Biomek i7 liquid handling platform. Finished libraries were quantified by Qubit fluorometer, Agilent TapeStation 2200, and RT-qPCR using the Kapa Biosystems library quantification kit according to manufacturer's protocols. Uniquely indexed libraries were pooled in equimolar ratios and sequenced on an Illumina MiSeq with paired-end 150bp reads by the Dana-Farber Cancer Institute Molecular Biology Core Facilities.

Sequencing data were aligned to the *Mus musculus* genome version 10 (mm10) using bwa-mem (v0.7.17) aligner[18] and converted to sorted BAM files with samtools (v1.10).[33] Duplicate reads in the BAM files were marked and tagged using Picard functionalities (v2.23.4). The base qualities of each read were recalibrated against known SNP databases using GATK (v4.1.6.0).[19] Variants were identified using MuTect2 (GATK) in 'single sample' mode with default parameters. The resulting variants were annotated with Ensembl Variant Effect Predictor (VEP) (v99) and reformatted with vcf2maf package (v1.6.16).[21,22]

X-ray, serum protein electrophoresis (SPE), and enzyme-linked immunosorbent assay (ELISA)

Radiographs of mouse forelimbs were acquired with a Faxitron X-ray cabinet (Model 43855A, Hewlett-Packard), on Oncology EDR2 film (Carestream) with 76 kVp x-ray tube energy, exposure times of 6 or 4 minutes (with or without musculature, respectively), and no magnification.

Plasma was isolated by centrifugation in Microtainer tubes (BD) and analyzed on SPIFE Serum Protein Gels with SPIFE 3000 (Helena Laboratories). Mouse VEGF (Sigma-Aldrich), IgM, and IgG (Innovative Research) ELISA Kits were used to assess plasma VEGF-A and immunoglobulin concentrations according to the manufacturers' protocols.

Proteomics

Sorted GC B-cells were washed in PBS and snap frozen in -80°C. Next, samples were resuspended in 5% sodium dodecyl sulfate and subjected to complete lysis and DNA shearing using a S220 Focused ultrasonicator (Covaris) in 1ml glass vials; reduced (tris(2-carboxyethyl)phosphine added to 20mM, 90°C for 20 minutes); cooled to room temperature (RT); and alkylated (iodoacetamide added to 50mM, RT in the dark for 30 minutes). Individual samples were subjected to detergent removal and enzymatic digestion using the S-Trap (ProtiFi); dried to near full dryness on a SpeedVac (Eppendorf); and resuspended in 100ul 50mM triethylammonium bicarbonate. Subsequently, samples were labeled with TMT10plex Isobaric Label Reagent Set (Thermo Scientific) for 1 hour at RT. Reaction was quenched with the addition of 5% hydroxylamine for 15 min. Labeled samples were then combined and fully dried in the SpeedVac. Combined peptides were separated on 1200 HPLC system (Agilent) using PolyWAX LP column (PolyLC; 200x2.1 mm, 5µm, 300Å) running under ERLIC (Electrostatic Repulsion-Hydrophilic Interaction Chromatography) mode conditions. Peptides were separated across 90 min gradient of buffer A (90% Acetonitrile (ACN), 0.1% Acetic Acid) and 0% to 75 % buffer B (30% Acetonitrile, 0.1% Formic Acid) with 20 fractions collected by time. Each fraction was dried in SpeedVac and re-suspended in 0.1% formic acid solution.

Each sample was submitted for single LC-MS/MS run on an LTQ Orbitrap Elite (Thermo Fischer) equipped with NanoAcquity HPLC pump (Waters). Peptides were separated in a 100 µm inner diameter microcapillary trapping column packed first with approximately 5 cm of C18 Reprosil resin (5 µm, 100 Å, Dr. Maisch GmbH, Germany) followed by analytical column ~20 cm of Reprosil

resin (1.8 µm, 200 Å, Dr. Maisch GmbH, Germany). Separation was achieved by a gradient of 5–27% ACN in 0.1% formic acid over 90 min at 200 nl/min. Electrospray ionization was enabled by applying a voltage of 1.8 kV using a home-made electrode junction at the end of the microcapillary column and sprayed from fused silica pico tips (New Objective). The LTQ Orbitrap Elite was operated in data-dependent mode. The mass spectrometry survey scan was performed in the Orbitrap in the range of 400 –1800 m/z at a resolution of 6×10^4, followed by the selection of the twenty most intense ions (TOP20) for CID-MS2 fragmentation in the ion trap using a precursor isolation width window of 2 m/z, AGC setting of 10,000, and a maximum ion accumulation of 200 ms. Singly charged ion species were not subjected to CID fragmentation. Normalized collision energy was set to 35 V and an activation time of 10 ms. Ions in a 10 ppm m/z window around ions selected for MS2 were excluded from further selection for fragmentation for 60 s. The same TOP20 ions were subjected to HCD MS2 event in Orbitrap part of the instrument. The fragment ion isolation width was set to 0.7 m/z, AGC was set to 50,000, the maximum ion time was 200 ms, normalized collision energy was set to 27V and an activation time of 1 ms for each HCD MS2 scan.

Raw data were submitted for analysis in Proteome Discoverer 2.4 (PD; Thermo Scientific) software. Assignment of MS/MS spectra was performed using the Sequest HT algorithm by searching the data against a protein sequence database including all entries from the Mouse Uniprot database (SwissProt 2017) and other known contaminants. Sequest HT searches were performed using a 20ppm precursor ion tolerance and requiring each peptides N/C termini to adhere with trypsin protease specificity, while allowing up to two missed cleavages. 10-plex TMT tags on peptide N termini and lysine residues (+229.162932 Da) was set as static modifications while methionine oxidation (+15.99492 Da) was set as variable modification. MS2 spectra assignment FDR of 1% on protein level was achieved by applying the target-decoy database search. Filtering was performed using a Percolator.[34] For quantification, a 0.02 m/z window centered on the theoretical m/z value of each of the ten reporter ions and the intensity of the signal

closest to the theoretical m/z value was recorded. The total signal intensity across all peptides quantified was summed for each TMT channel, and all intensity values were adjusted to account for potentially uneven TMT labeling and/or sample handling variance for each labeled channel.

The spectrum search results with PD were read into R[27] and filtered against a list of common contaminants. Data structures provided by the MSnbase library[35] in R/Bioconductor[36] were used to represent the filtered matrix, which provided convenient functions for data manipulation and visualization. Data matrix was normalized with a MSnbase wrapper function that uses the vsn R/Bioconductor library.[37] Normalization step was validated with a principal component analysis (PCA) and the first 2 components were used to visually inspect the separation between *WT* and *KO* samples. Unwanted variation was removed by adding latent model terms to the model equation. The additional parameters were determined from the residuals of a regression analysis. Proteins differentially expressed (DE) between *WT* and *KO* samples were the result of applying a linear model to the abundance data and contrasting on the *WT* versus the *KO* using the limma library[38] of R/Bioconductor.

miR target enrichment was performed on proteins upregulated (FDR<0.1) in GC B-cells from *KO* compared to *WT* mice using MIENTURNET and TargetScan database.[39,40] Metaspace[41] was used for functional enrichment and interactome analysis of DE proteins (FDR<0.1) using recommended settings. Differential expression analysis of microarray data was used to determine genes upregulated in light zone (LZ up) vs dark zone (DZ up; GSE38696,[42] FDR<0.1; top 150 fold-changed probes, given the limited number of DE genes between LZ and DZ cells) and GC (GC up) vs plasma cells (PC up; GSE11961,[43] FDR<0.01, top 400 fold-changed probes). Gene set enrichment analysis[44] of these genesets and the 'hallmark' genesets from MSigDB[45] was run using recommended settings. R[27] packages were used to visualize the data: pheatmap[46] for heatmap, ggplot2[28] for PCA, DE, and GSEA bubble plots as well as miR target enrichment bar plot, and Rtoolbox (https://github.com/PeeperLab/Rtoolbox) for GSEA mountain plots.

Supplemental Tables

Supplemental Table 1. Primary antibodies

Antigen	Application	Source	Catalog number
B220 (mouse)	IHC	BD Biosciences	550286
BCL2 (mouse)	IHC/ Immunoblotting	Abcam	ab182858
BCL6 (mouse)	IHC	Santa Cruz Biotechnology	sc-858
CD10 (human)	IHC	Leica Biosystems	NCL-L-CD10-270
CD138 (human)	IHC	Beckman Coulter	PN IM2757
CD138 (mouse)	IHC	BD Biosciences	553712
CD21 (mouse)	IHC	Dako	M0784
CD3 (mouse)	IHC	Dako	A0452
CD5 (mouse)	IHC	Sino Biological	50403-RP02-50
Cleaved caspase 3 (mouse)	IHC	Cell Signaling Technology	9664
Cre (mouse)	IHC	Millipore	69050
pERK (mouse)	IHC	Cell Signaling Technology	4370
IgG (mouse)	IHC	SouthernBiotech	1070-01
IgM (mouse)	IHC	SouthernBiotech	1020-01
Kappa (mouse)	IHC	SouthernBiotech	1170-01
Ki-67 (mouse)	IHC	Vector Laboratories	VP-K451
Lambda (mouse)	IHC	SouthernBiotech	1175-01
MYC (mouse)	IHC	Abcam	ab32072
PAX5 (mouse)	IHC	Cell Signaling Technology	12709
PD-1 (human)	IHC	Cell Marque	315M-95
VEGF-A (mouse)	IHC	Abcam	ab52917
CD138 (human)	IF	Bio-Rad Laboratories	MCA2459GA
B220 (mouse)	FACS	BD Biosciences	553087
CD138 (mouse)	FACS	BD Biosciences	553714
CD21/CD35 (mouse)	FACS	BioLegend	123418
CD23 (mouse)	FACS	BioLegend	101618
CD3 (mouse)	FACS	eBioscience	17-0031-83
CD38 (mouse)	FACS	BioLegend	102720
CD86 (mouse)	FACS	BioLegend	105007
CD95 (mouse)	FACS	BD Biosciences	557653
CXCR4 (mouse)	FACS	eBioscience	17-9991-80
Actin (mouse)	Immunoblotting	Santa Cruz Biotechnology	sc-1615
CHEK1 (mouse)	Immunoblotting	Santa Cruz Biotechnology	sc-8408
Cyclin-D2 (mouse)	Immunoblotting	Santa Cruz Biotechnology	sc-593
Cyclin-E1 (mouse)	Immunoblotting	Cell Signaling Technology	20808

Supplemental Table 2. Oligonucleotide sequences and TaqMan assays

Oligonucleotide	Application	Sequence (5' → 3')/Assay ID	Source
LNA-miR-15a	ISH	DIG-CACaaAcCatTatgTgctGcta	Bio Basic
LNA-miR-15b	ISH	DIG-TGTaaAcCatGatgTgctGcta	Bio Basic
LNA-miR-16	ISH	DIG-cgcCaatAtTtAcGtgCtGcTa	Bio Basic
V_HJ558a (forward)	Mutation analysis	SAGGTCCAGCTGCAGCAGTCTGG	IDT
V_HQ52 (forward)	Mutation analysis	CAGGTGCAGCTGAARCAGTCA	IDT
V_H36-60/4 (forward)	Mutation analysis	GAGGTGMAGCTTCYSGAGTC	IDT
V_H7183b (forward)	Mutation analysis	GTGAAGCCTGGAGGGTCCC	IDT
V_H7183c (forward)	Mutation analysis	GGCTTAGTGMAGCCTGGAGG	IDT
V_H6/7 (forward)	Mutation analysis	GAGGTGAAGCTKGYGGAGTCT	IDT
V_HGam3.8 (forward)	Mutation analysis	CAGATCCAGTTGGTRCAGTCT	IDT
JH4int2 (reverse)	Mutation analysis	ACTATCCCTCCAGCCATAGG	IDT
miR-15a	RT-qPCR	000389	TaqMan
miR-15b	RT-qPCR	000390	TaqMan
miR-16	RT-qPCR	000391	TaqMan
snoRNA234	RT-qPCR	001234	TaqMan
U6	RT-qPCR	001973	TaqMan

Supplemental Table 3. Differentially expressed proteins between GC B-cells from *KO* and *WT* mice (FDR<0.1)

Protein ID	logFC	P.Value	adj.P.Val
Q8BX57	0.542415296	6.56E-08	0.000245625
Q8R2K4	-0.285471243	1.90E-07	0.000245625
Q920A7	-0.331438319	1.70E-07	0.000245625
P58871	-0.455588746	6.76E-07	0.000655451
Q61704	0.338861714	1.30E-06	0.001010369
Q9D084	0.568352367	6.76E-06	0.002623497
Q8BG32	-0.155876073	6.44E-06	0.002623497
Q9CRC8	-0.184341255	4.52E-06	0.002623497
P61358	-0.186470332	5.10E-06	0.002623497
Q8K4Q7	-0.247010724	6.37E-06	0.002623497
Q9D187	0.208342195	8.28E-06	0.002921554
Q8R4K2	-0.346631241	1.23E-05	0.003961302
P40336	0.373021651	1.82E-05	0.004151638
Q9DB40	0.214146466	1.78E-05	0.004151638
Q63844	0.1694589	1.68E-05	0.004151638
Q9CR11	0.161355898	1.61E-05	0.004151638
Q9R0Q6	-0.202665845	1.69E-05	0.004151638
P97465	0.195506441	2.10E-05	0.004427469
Q8CE64	-0.193364589	2.17E-05	0.004427469
Q99PT1	0.160027541	2.53E-05	0.004471782
P15508	0.148931249	2.47E-05	0.004471782
Q8K3H0	-0.231713971	2.54E-05	0.004471782
Q60649	-0.249692844	2.70E-05	0.004561472
P35980	-0.170808869	2.89E-05	0.004606872
Q9D8V0	-0.296361201	2.97E-05	0.004606872
Q80U49	0.119550921	4.24E-05	0.006329608
Q8BFQ8	0.131647128	4.50E-05	0.006470541
Q9CR80	0.119737325	4.68E-05	0.006489895
Q923D2	0.143728952	6.34E-05	0.008091648
P23198	0.134750463	7.09E-05	0.008091648
Q9D1R9	-0.11248519	7.03E-05	0.008091648
Q922X9	-0.166441294	6.67E-05	0.008091648
Q7TSJ6	-0.189477062	6.32E-05	0.008091648
Q99KN2	-0.447081691	6.73E-05	0.008091648
P21107	0.216614289	8.64E-05	0.00894771
P49710	0.148514472	8.53E-05	0.00894771
Q9JIH2	0.134846018	8.76E-05	0.00894771
Q9QZE7	-0.376461444	8.25E-05	0.00894771
Q497H0	0.141426005	9.07E-05	0.009026114
Q9D8T2	0.210358071	9.81E-05	0.009172107
Q8K1L5	0.181516079	0.000106343	0.009172107
Q9DBU0	0.163428184	0.00010493	0.009172107
A2AR02	0.132090828	0.000109733	0.009172107
P42232	-0.184751234	0.000107574	0.009172107
Q6GYP7	-0.189412181	0.000111105	0.009172107
Q9R0P5	-0.206914708	0.000102056	0.009172107
Q8CGP0	-0.211811826	9.49E-05	0.009172107
Q8K0U4	0.321382672	0.000116581	0.009185377
P29758	0.108501667	0.000115006	0.009185377
E9Q7E2	-0.162418952	0.000120736	0.009185377
Q8C1Q6	-0.256954824	0.000119864	0.009185377
Q3U821	-0.301225318	0.000124133	0.009262247
O70220	0.247119532	0.000136553	0.009996713
Q61712	0.214340713	0.00016185	0.010106135
Q91W18	0.189921179	0.000160539	0.010106135
P09926	0.171627331	0.000163556	0.010106135

P26369	0.157728877	0.000167637	0.010106135
Q60821	0.151884858	0.000148637	0.010106135
P17225	-0.118632206	0.000149473	0.010106135
Q8CBW3	-0.14796551	0.000147843	0.010106135
Q9JHK4	-0.17078366	0.000169304	0.010106135
Q9CZM2	-0.179404557	0.000160563	0.010106135
Q8K4B0	-0.180070899	0.000169214	0.010106135
Q9CR02	-0.292703602	0.000144054	0.010106135
Q8BPB0	-0.356532075	0.000156748	0.010106135
Q9CQ36	-0.332649006	0.000177238	0.010419426
P97386	-0.233801309	0.000184344	0.010675452
E9Q309	-0.126994093	0.000190617	0.010718777
Q8BH59	-0.205371277	0.000188227	0.010718777
Q6ZQ08	-0.141262364	0.000197663	0.010956187
Q8VE97	0.123729211	0.000211487	0.011557314
Q99P21	0.378562956	0.00022909	0.01156051
Q80VR2	0.210521757	0.000216144	0.01156051
Q9CXG9	0.176755978	0.000217564	0.01156051
Q8JZK9	0.131030072	0.000226906	0.01156051
O35955	0.1306033	0.000229423	0.01156051
Q9CR57	-0.135680775	0.000228869	0.01156051
Q02819	0.126544114	0.000233327	0.011606506
Q8VE92	0.160112671	0.000238213	0.011697957
O70338	-0.177785165	0.000241195	0.011697957
Q61599	0.173687646	0.000269903	0.012928692
Q91Z53	0.203369854	0.000277632	0.012965045
Q9DBM1	-0.125241979	0.000284028	0.012965045
Q11011	-0.144971699	0.000283552	0.012965045
P97930	-0.176025734	0.000279128	0.012965045
B2RQC6	-0.173075057	0.00030122	0.013589916
Q6PDY2	0.125748856	0.000309872	0.013662558
Q8BSS9	0.1036784	0.000309112	0.013662558
O88291	0.107013765	0.000320383	0.013967278
A6H8H2	-0.269568561	0.000329324	0.014197532
Q64518	-0.112139491	0.000340034	0.014498148
P19253	-0.149169478	0.000349589	0.014743538
P80315	-0.115437966	0.000359794	0.014919153
Q9Z0R0	-0.387038739	0.000361443	0.014919153
Q9JK23	-0.151592783	0.00037444	0.015133611
Q8R060	-0.256585221	0.000371335	0.015133611
O88967	-0.260847166	0.000388865	0.015554585
P83917	0.200211029	0.00039816	0.015763885
Q8K4K6	0.204824107	0.000433665	0.015992387
P57759	0.124598898	0.00041572	0.015992387
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Q7TPS5	-0.342690017	0.000422002	0.015992387
Q9WV60	-0.108499243	0.000444458	0.016116808
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Q8BQ30	0.275653979	0.000493177	0.016639365
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Q8BHJ9	0.132980532	0.000510938	0.016943923
Q91ZE0	0.189633751	0.000526295	0.017106234

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Q3UHC0	0.214365811	0.000539717	0.017220964
Q8CG46	-0.130189064	0.000541484	0.017220964
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P60762	0.134991115	0.005648741	0.053983038
Q61768	0.082477744	0.005698675	0.054326439
P00493	-0.1112715	0.005730142	0.054359295
Q8CI33	-0.284186667	0.005720832	0.054359295
Q91WG8	0.147257034	0.005821421	0.054614568
P09450	0.111088047	0.005776987	0.054614568
Q9D6J6	0.108514946	0.005794966	0.054614568
Q9JHS9	0.086137993	0.00580551	0.054614568
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Q9R1Q7	-0.223834288	0.005882022	0.054861171
P62717	-0.098108506	0.00594109	0.055279206
Q9Z2D6	0.233124675	0.005973708	0.055317391
P83887	-0.142855405	0.005969057	0.055317391
Q8C2K5	0.066568104	0.006007289	0.055495911
Q6P5B0	-0.076461452	0.006041839	0.055682504
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P23249	0.299622233	0.006104106	0.05592182
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P62305	-0.124350003	0.006115619	0.05592182
P41230	-0.131744741	0.006154283	0.05592182
O08810	-0.234911842	0.006128655	0.05592182
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Q9D162	-0.188246928	0.006219915	0.056254708
E9PVA8	-0.108343365	0.006237455	0.056282155
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Q99L27	0.083080182	0.006306666	0.056652999
Q8BWY3	-0.16606388	0.0063208	0.056652999
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P62245	-0.139479515	0.006440964	0.05714029
P56135	-0.196677658	0.006462368	0.05714029
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P14824	0.141907777	0.006608647	0.057500446
P06151	-0.138548596	0.006586481	0.057500446
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Q61097	0.181947133	0.006817249	0.05831207
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Q80VH0	0.068647216	0.006972071	0.059193949
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Q8BMS1	-0.099656641	0.007044618	0.059679301
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Q6ZWV3	-0.131906538	0.007112405	0.059861457
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Q8R4H2	0.129240683	0.007484721	0.061144147
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Q91YR1	-0.119269653	0.009174637	0.068588806
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P24547	-0.07559976	0.012042973	0.077565351
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Q8CDD9	0.176076683	0.016451084	0.093046948
Q61216	0.052124393	0.016592294	0.093709028
Q9QYR9	0.116007203	0.016651081	0.093768059
Q9CZB3	-1.191781915	0.01664472	0.093768059
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P68254	0.129371087	0.016724341	0.093908024
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P62889	-0.085139516	0.017261279	0.096088615
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Q9CQH3	-0.153971401	0.017796179	0.098360648
Q8CAY6	-0.098745143	0.017824141	0.098375058
Q8CI75	0.083971105	0.017911437	0.098592284
Q9Z140	-0.362376991	0.01791432	0.098592284
Q6P4S8	0.11934236	0.018064782	0.098859453
Q61142	0.072591719	0.018048874	0.098859453
Q9ERD6	-0.075062808	0.018030394	0.098859453
Q9R0Q1	-0.406327537	0.018026629	0.098859453
P58501	-0.101009474	0.018178983	0.099344301

Supplemental Table 4. Summary of *VDJ* recombination and somatic hypermutation analysis in *KO* mice with indicated lymphoma phenotypes

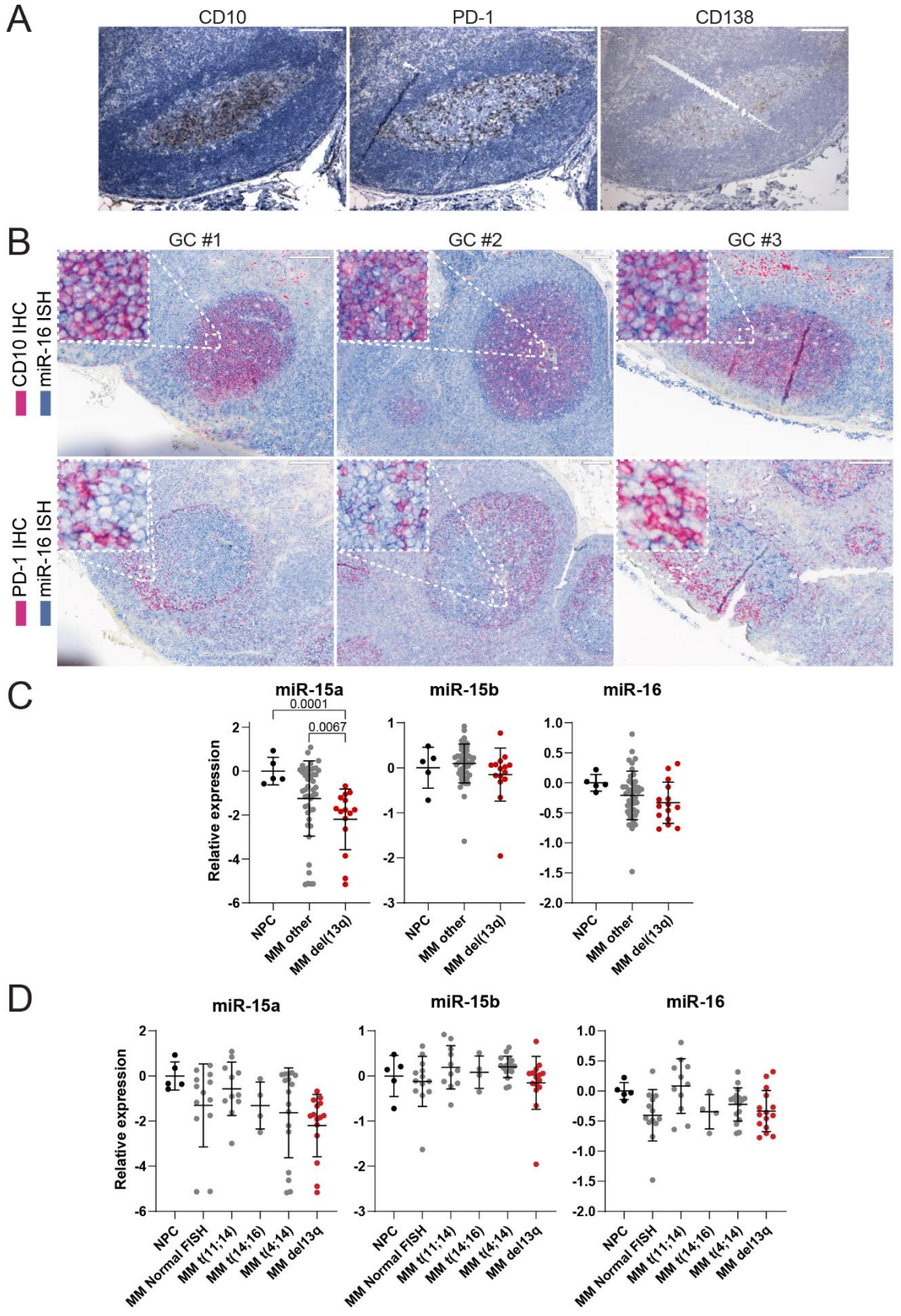
Diagnosis	Mouse No	VH	DH	JH	VH mut.
FL	FL_1	IGHV5-17*01 F	IGHD1-1*01 F	IGHJ1*03 F	1
	FL_2	IGHV1-76*01 F	IGHD2-4*01 F	IGHJ4*01 F	13
	FL_3	IGHV2-9-1*01 F	IGHD3-1*01 F	IGHJ4*01 F	2
DLBCL	DLBCL_1	IGHV5-6*02 [F] or IGHV5-6*03 [F]	IGHD4-1*01 F	IGHJ1*03 F	4
	DLBCL_2	IGHV1-47*01 F	IGHD3-2*01 F	IGHJ2*01 F	31
	DLBCL_3	IGHV9-3*01 F	IGHD4-1*01 F	IGHJ4*01 F	1
EP	PC_1	IGHV2-2*01 F	IGHD2-4*01 F	IGHJ4*01 F	7
	PC_2	IGHV9-3*01 F	IGHD4-1*01 F	IGHJ4*01 F	2 or 0*
	PC_3	IGHV12-3*01 F	IGHD2-3*01 F	IGHJ4*01 F	6

*6 of 9 screened colonies harboring immunoglobulin region had mutations, 3 didn't

Supplemental Table 5. Summary of somatic mutations in GC B-cells from 12-week old *KO* mice and spleens from *KO* mice that did not develop neoplasms

Gene	Sample	Protein changes of variants that passed MuTect2 Filters (VAF)
Gna13	*KO* GC B-cells #1	-
	KO GC B-cells #2	-
	KO GC B-cells #3	p.R69W (0.37%), p.G111Efs*12 (0.51%), p.M136V (0.44%)
	KO spleen #1	-
	KO spleen #2	-
	KO spleen #3	p.T352Rfs*17 (1.07%)
Hist1h1c	*KO* GC B-cells #1	-
	KO GC B-cells #2	-
	KO GC B-cells #3	-
	KO spleen #1	-
	KO spleen #2	-
	KO spleen #3	-
Hist1h1e	*KO* GC B-cells #1	-
	KO GC B-cells #2	-
	KO GC B-cells #3	-
	KO spleen #1	-
	KO spleen #2	-
	KO spleen #3	-
Pim1	*KO* GC B-cells #1	-
	KO GC B-cells #2	-
	KO GC B-cells #3	-
	KO spleen #1	p.S54P (1.62%)
	KO spleen #2	p.A224T (0.94%)
	KO spleen #3	p.K94R (0.71%), p.I248T (1.2%)

Supplemental Figures



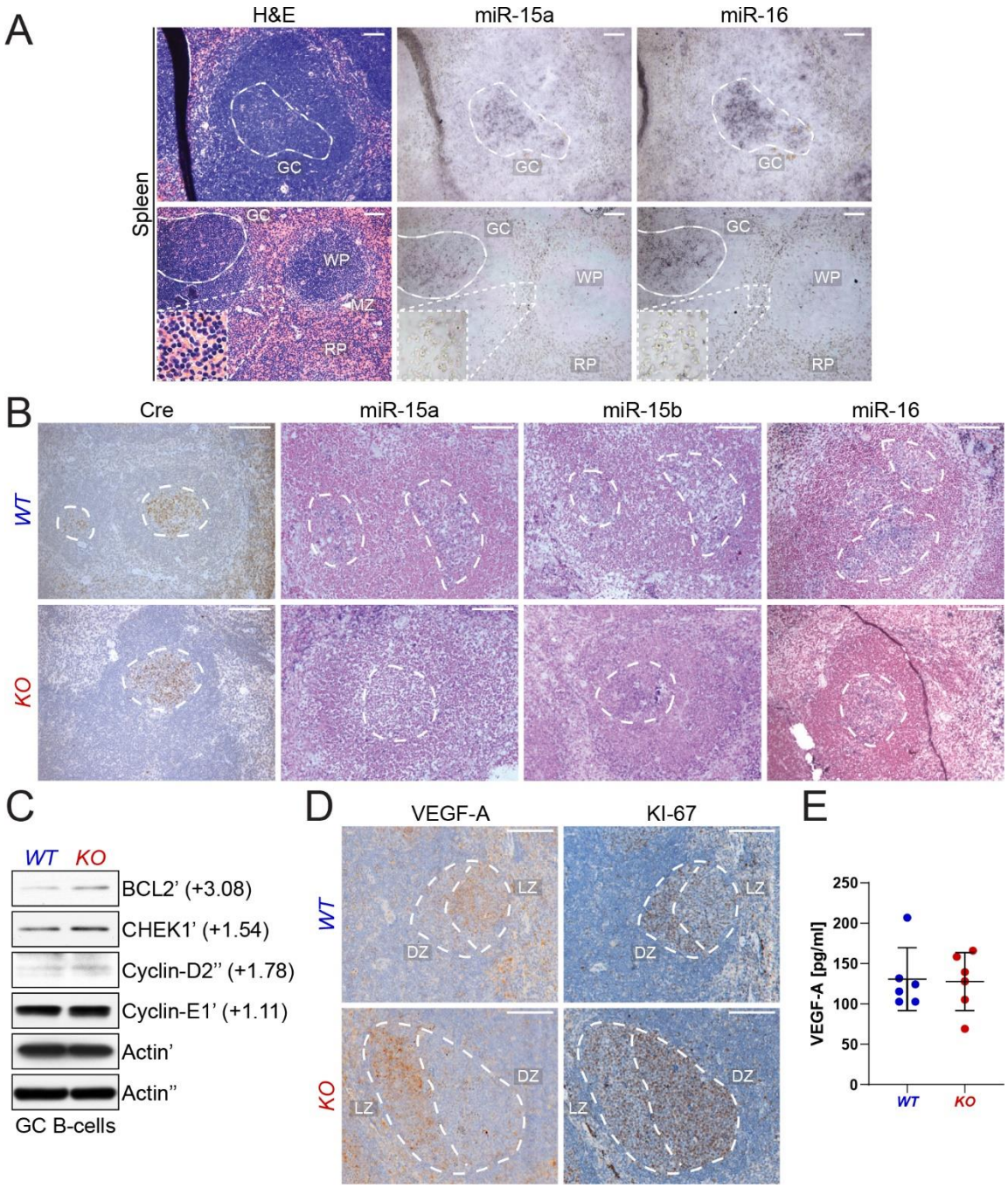
Supplemental Figure 1. miR-15a and miR-16 expression in human GCs and MM cells

(A) IHC analysis of CD10, PD-1, and CD138 expression in LNs from a normal subject. Note that most cells within the GC are $CD10^+$ GC B-cells varyingly infiltrated by PD-1^+ T_{FH}-cells and $CD138^+$ PCs. H&E, hematoxylin and eosin. Scale bar = 200μm.

(B) miR-16 co-localization with GC B-cell marker CD10 and T_{FH}-cell marker PD-1 in human LNs. miR-16 expression was assessed by ISH (dark purple), followed by IHC analysis for CD10 or PD-1 (red) on the same FFPE slide. Three representative examples are shown. Note co-localization of miR-16 signal and CD10 in GC B-cells as well as PD-1 in T_{FH}-cells. Scale bar = 200μm.

(C) miR-15a, miR-15b, and miR-16 levels in BM $CD138^+$ cells from healthy donors (normal plasma cells; NPC) and MM patients without (other) or with del(13q) from GSE16558. Graphs depict the mean ±SD. *P* values were calculated using Mann–Whitney *U*-test.

(D) miR-15a, miR-15b, and miR-16 levels in BM $CD138^+$ cells from healthy donors (normal plasma cells; NPC) and MM patients with indicated alteration. Graphs depict the mean ±SD.



Supplemental Figure 2. miR-15a/16 and their targets expression in murine GCs

(A) Histologic and ISH analysis of miR-15a and miR-16 expression in the spleen of wild-type mouse. Note higher miR-15a and miR-16 expression in GCs within white pulp (WP) areas and lower expression in marginal zone (MZ) or follicular (Fo) B-cells. Note that birefringent red blood

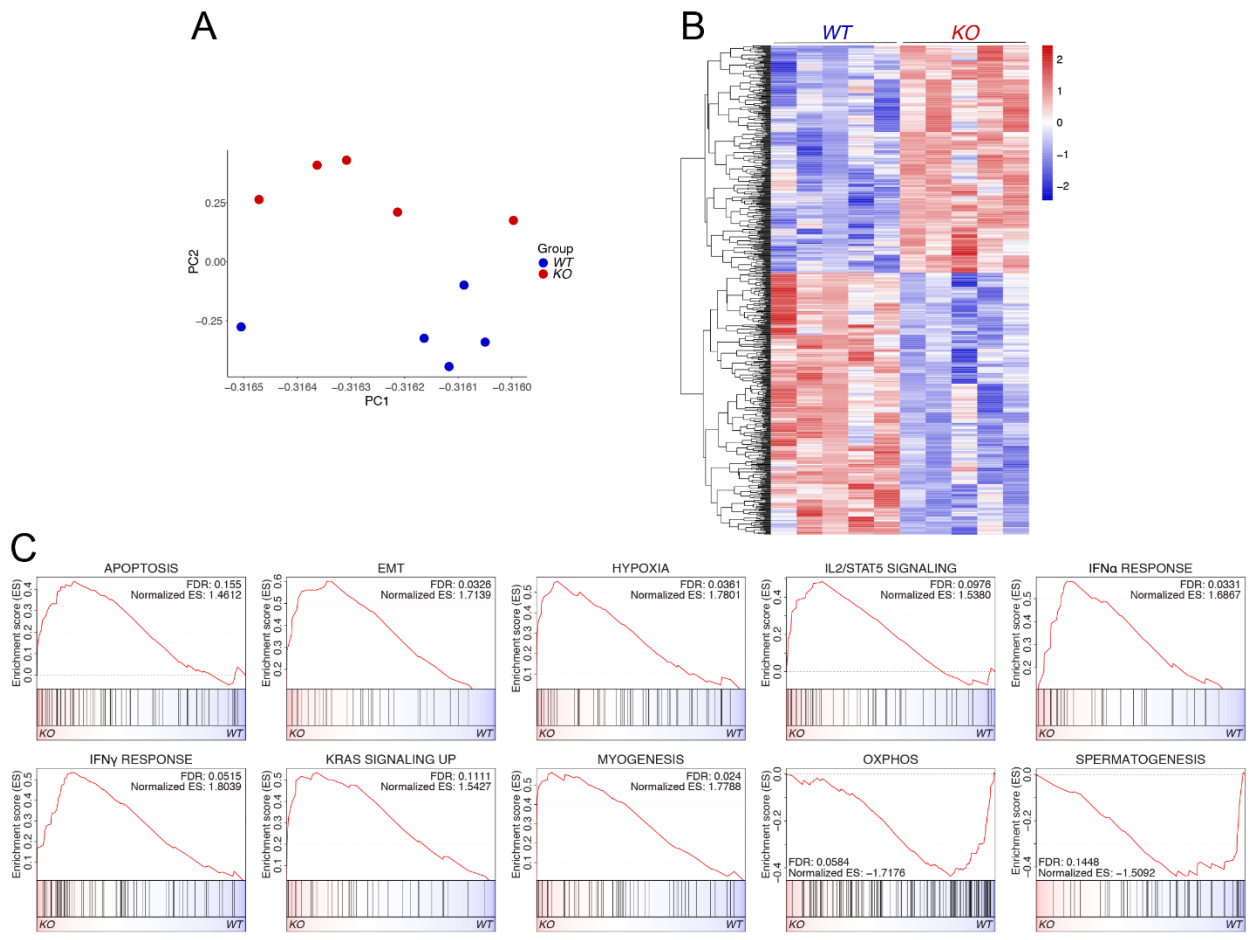
cells in the red pulp (RP) area (insert) refract the light but do not stain positive for miR-15a or miR-16. H&E, hematoxylin and eosin. Scale bar = 50μm.

(B) Cre (IHC, brown) and miR-15a, miR-15b, and miR-16 expression (ISH, dark purple) in spleen sections of 12-week old *WT* and *KO* mice. One representative example of secondary follicle for each genotype is shown. Sections were counterstained with Giemsa (IHC) or Fast Red (ISH) to better identify lymphoid structures. GCs are highlighted by dotted lines, scale bars = 100μm.

(C) Changes in miR-15a/16 target genes expression after *miR-15a/16-1* cluster deletion in FACS-sorted GC B-cells ($B220^{+}CD95^{+}CD38^{-}$) from mice with indicated genotypes assessed by immunoblotting. Quantitative differences in protein expression level based on densitometric analysis were normalized to actin and are shown in parentheses.

(D) IHC analysis of VEGF-A and Ki-67 expression within splenic GCs from mice with indicated genotypes. Note high and low VEGF-A abundance within the light zone (LZ) and the dark zone (DZ), respectively. Scale bar = 100μm.

(E) Plasma VEGF-A concentrations assessed using ELISA in *WT* (n=6) and *KO* (n=6) mice immunized with SRBC. Graphs depict the mean ±SD.

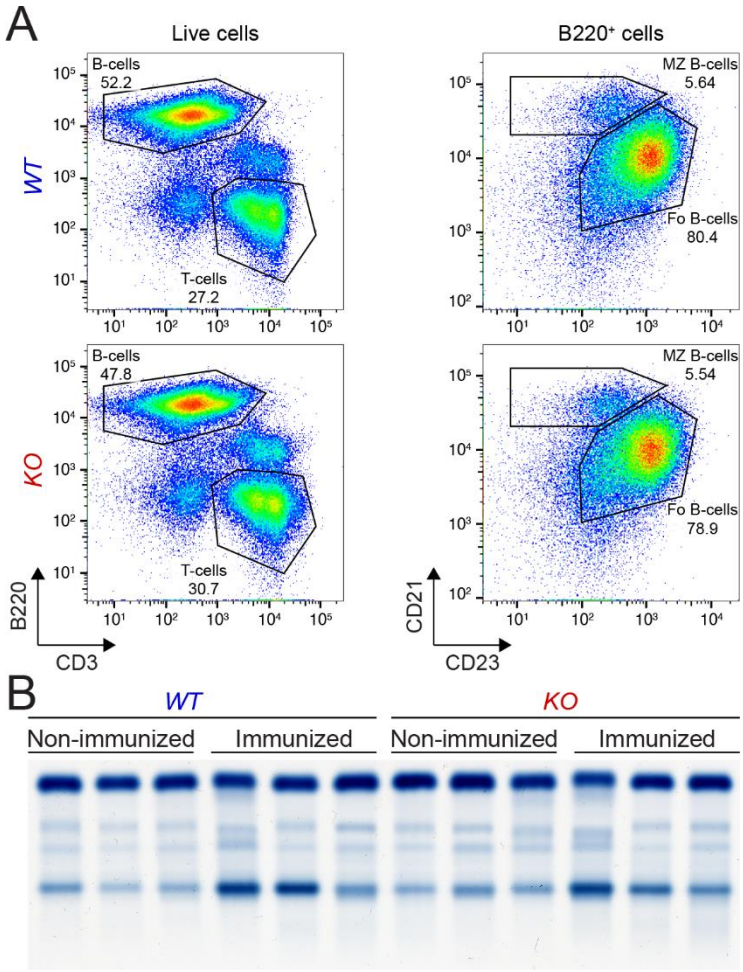


Supplemental Figure 3. Analyses of proteomic changes induced by *miR-15a/16-1* loss in GB B-cells

(A) Principal component analysis (PCA) plot of protein expression profiles of GC B-cells from *WT* (n=5) and *KO* (n=5) mice.

(B) Heatmap showing proteins differentially expressed between *WT* and *KO* GC B-cells (n=5 per group).

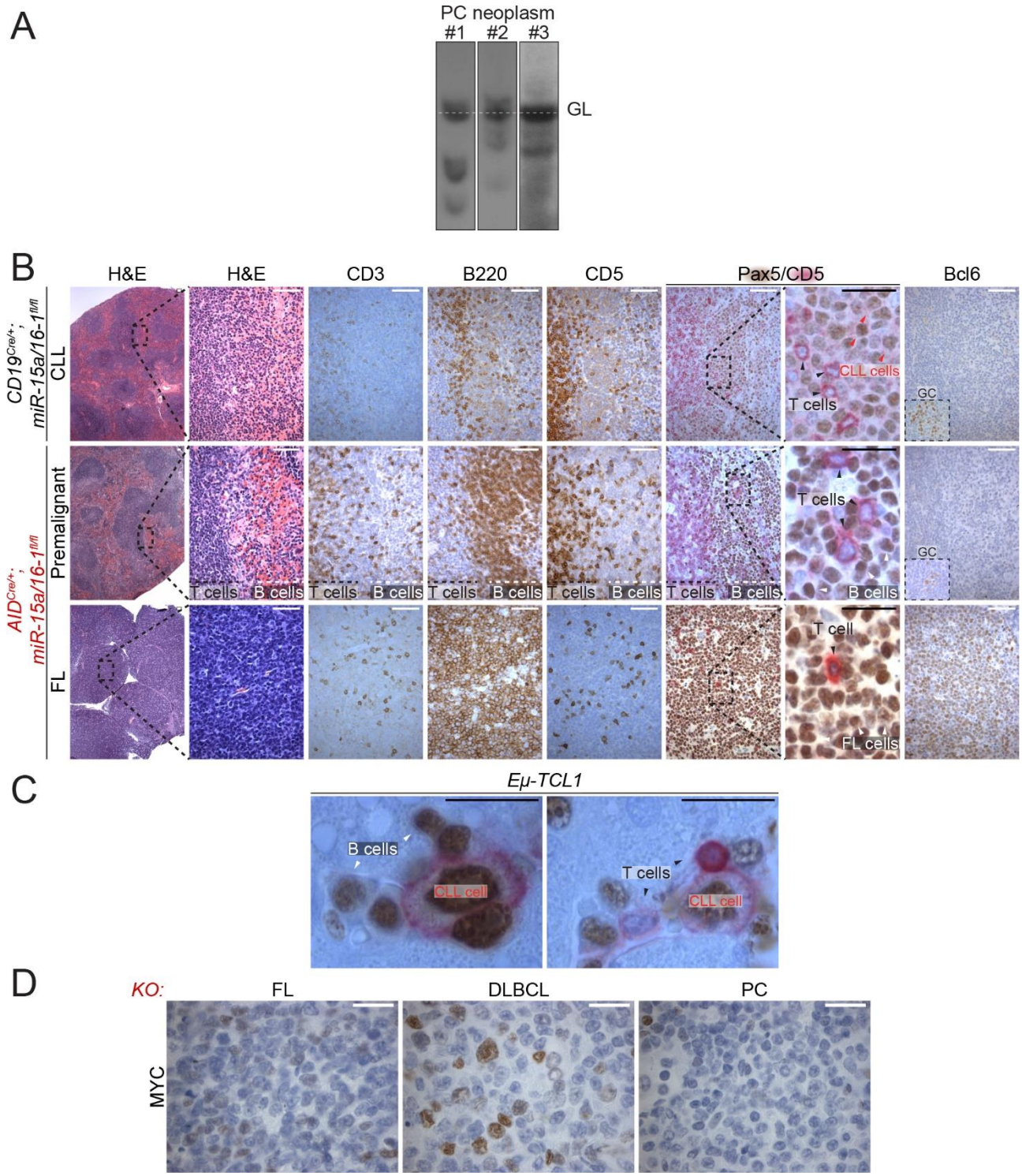
(C) GSEA mountain plots of 'hallmark' genesets enriched in *WT* or *KO* GC B-cells at FDR<0.2.



Supplemental Figure 4. Analyses of serum proteins and lymphocyte subpopulations in *WT* and *KO* mice

(A) Flow cytometric analysis of indicated lymphocyte subsets in the spleen of *WT* and *KO* mice immunized with SRBC. Three animals per group were analyzed. Representative dot plots are shown.

(B) Serum protein electrophoresis of young non- and SRBC-immunized *WT* and *KO* mice.



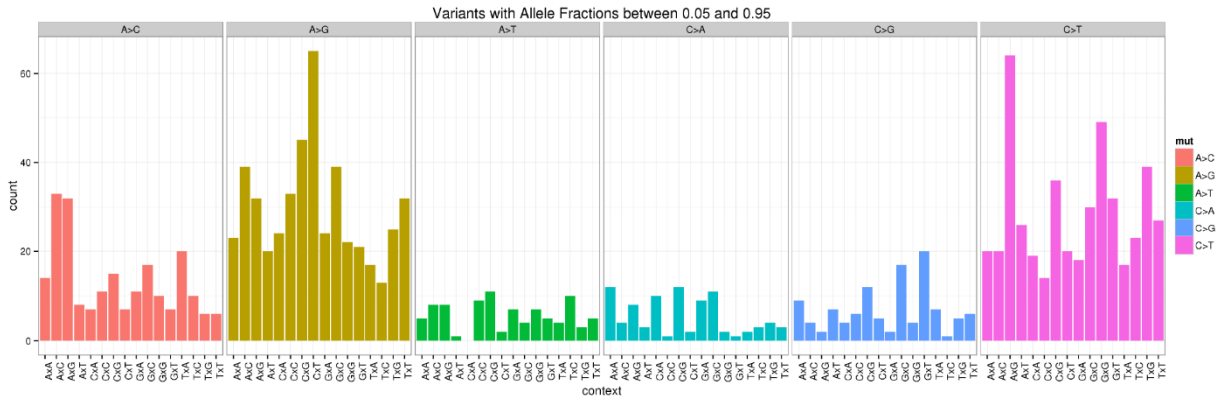
Supplemental Figure 5. Clonality evaluation and immunophenotypic comparison of low-grade lymphomas in *AID$^{Cre/+}$;miR-15a/16-1$^{fl/fl}$* and *CD19$^{Cre/+}$;miR-15a/16-1$^{fl/fl}$* mice

(A) Clonality evaluated by Southern blot analysis of the *IgH* gene in DNA isolated from spleens of *KO* mice with the plasma cell (PC) neoplasm. The non-rearranged germ line (GL) band (dashed gray line) and clonally rearranged bands were identified (arrowheads).

(B) Histologic and IHC stains of indicated markers on serial sections from a spleen of *CD19$^{Cre/+}$;miR-15a/16-1$^{fl/fl}$* mouse with CLL (top) and from a spleen of premalignant (middle) or a LN of FL-bearing (bottom) *AID$^{Cre/+}$;miR-15a/16-1$^{fl/fl}$* mouse. Pictures were taken at the junction between the T-cell and B-cell rich areas. H&E, hematoxylin and eosin. Scale bars: white = 50μm; black = 20μm.

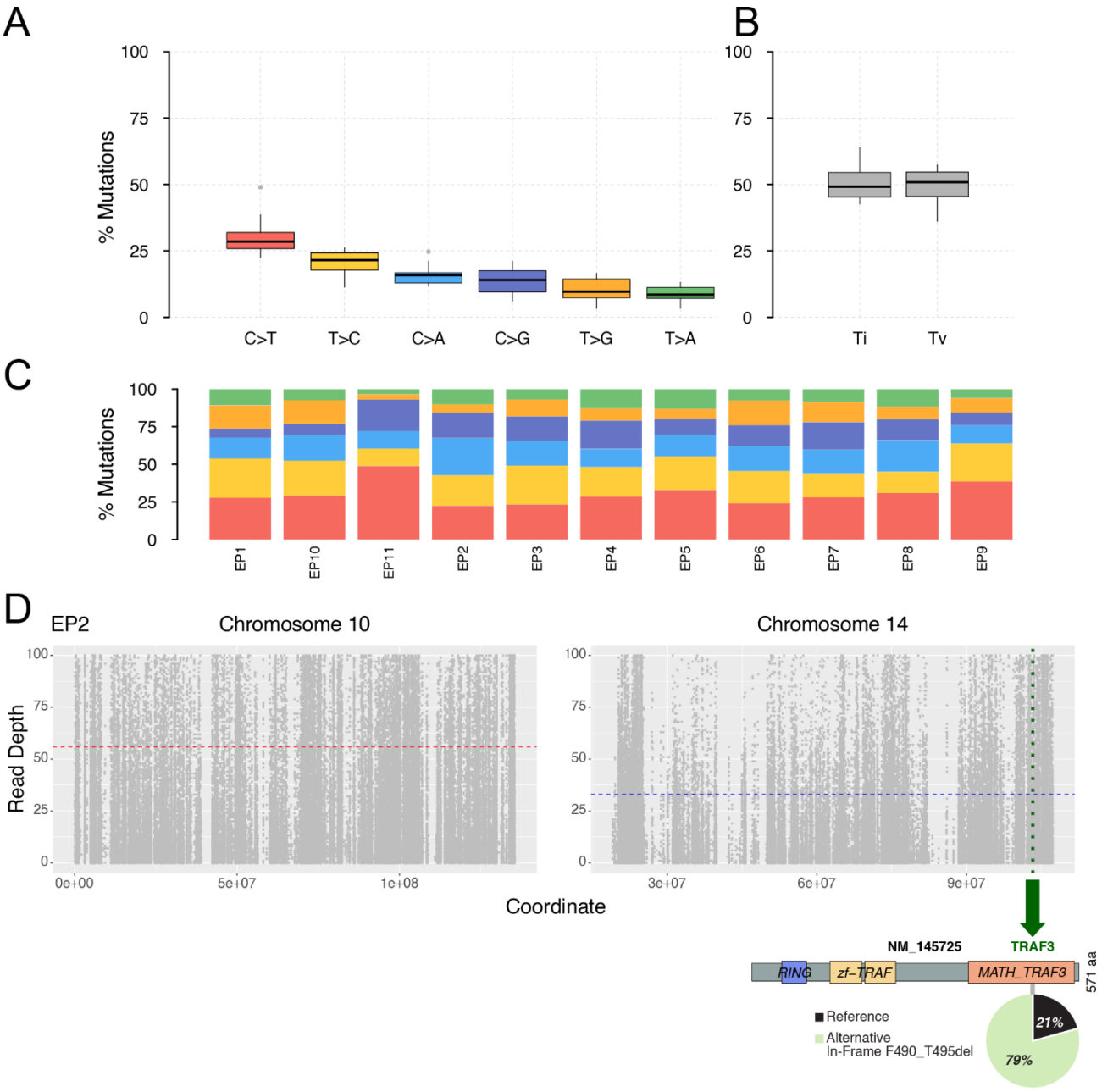
(C) Specificity validation of IHC double-stain for mouse PAX5 (brown, nuclear) and CD5 (red, membrane) in *Eμ-TCL1* mouse.[47] Note red membrane and brown nuclear signal characteristic for CLL cells and single red or brown staining for B-cells and T-cells respectively. Scale bar = 20μm.

(D) IHC stains of MYC from representative *KO* mice with the indicated lymphoma phenotype. Scale bar = 20μm.



Supplemental Figure 6. WES analysis of murine neoplasms from *KO* mice

Mutation frequencies in the PC neoplasm and DLBCL from *KO* mice determined using WES. Variants with allele fractions between 0.05 and 0.95 are shown.

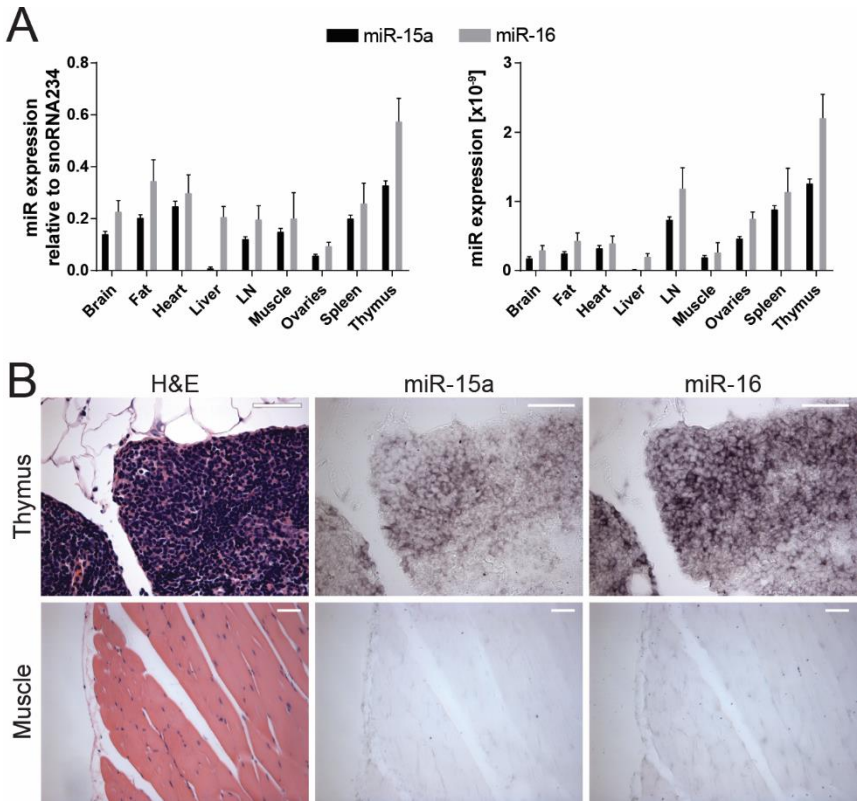


Supplemental Figure 7. WES analysis of human EP

(A), **(B)**, and **(C)** Summary of transition and transversion frequencies in human EP (n=11) determined using WES. Box plots show summary for six different conversions **(A)** and transitions vs transversions **(B)**, whereas bar plot shows fractions in each sample **(C)**.

(D) Representative case (EP2) of biallelic *TRAF3* inactivation. Top: plots illustrating the coverage of chromosomes 10 and 14. Red and blue dashed lines indicate mean coverage. Note almost

50% reduction of the mean coverage for chromosome 14, compared to diploid chromosome 10, suggesting a clonal loss. Dark green dashed line indicates location of *TRAF3* on chromosome 14. Bottom right: location of the *TRAF3* mutation in EP2 and its variant allele frequency (VAF) illustrated as a pie chart. Given the limited purity of FFPE samples, this VAF also suggests a clonal alteration; altogether indicating biallelic mechanism of inactivation.



Supplemental Figure 8. miR-15a and miR-16 expression pattern in mice

(A) miR-15a and miR-16 expression determined using RT-qPCR relative to snoRNA234 (right) or unnormalized (left) in indicated tissues from a wild-type mouse. Error bars represent standard deviation of three independent replicates in a representative experiment.

(B) Histologic and ISH analysis of miR-15a and miR-16 expression in thymus and muscle used as positive and negative controls, respectively, during all ISH studies. H&E, hematoxylin and eosin. Scale bar = 50μm.

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