Supplemental Materials and Methods

Flow cytometry and cell sorting

All flow cytometry and cell sorting experiments were performed using ARIA III (BD) and Celesta (BD). For staining of extracellular markers, cell suspensions were incubated with the following antibodies (Cat#/clone): Ter119 (116206/TER-119), CD16/32 (101306/93, 101317/93), Gr1 (108406/RB6-8C5), B220 (103206/RA3-6B2), CD3e (100204/17A2, 100334/145-2C11, 100329/145-2C11), CD34 (128608/HM34), CD150 (115909/TC15-12F12.2), CD48 (103426/HM48-1), Sca-1 (122512/E13-161.7, 108127/D7), c-Kit (105813/2B8, 105808/2B8), Ly6G (127608/1A8), Ly6C (128032/HK1.4, 128033/ HK1.4), CD11b (101212/M1/70, 563168/M1/70), CXCR4 (146506/L276F12), CD45 (103112/30-F11), CD45.1 (560578/A20), CD45.2 (109826/104), 7-AAD Viability Staining Solution (420404) (Biolegend). Flow cytometry data were analyzed with FlowJo v.10.

RNA extraction, RNA sequencing and computational analysis

HSPCs were sorted from the BM and spleen, either treated with β-glucan or PBS. RNA was extracted using the PicoPure kit (#KIT0204, ARCTURUS) according to the manufacturer's instructions. Then, a DNA-free kit (#AM1906, Thermo Fisher) was used to remove any DNA traces from the samples. mRNA libraries were generated using the Illumina TruSeq Sample Preparation kit v2 (#RS-122-2001). Single-end 75-bp mRNA sequencing was performed on Illumina NextSeq 500. Quality of sequencing was assessed using FastQC software [1]. Raw reads in fastq format were collected and aligned to the mouse genome (mm10 version) and human genome (hg38 version) using STAR 2.6 algorithm[2]. Gene quantification was performed using HTSeq [3] using Gencode annotation (v.M19 for mouse and v.29 for human data) and differential expression analysis was performed using edgeR package[4] (glmFit model) in R [5]. Genes with a FoldChange|(FC)|≥1.5 & p-value<0.05 were considered statistically significantly up- and down-regulated respectively. Volcano plots were created in R.

Enrichment analysis

Differentially expressed genes (DEGs) were used for gene ontology (GO) analysis using g:Profiler web-server [6]. Gene Set Enrichment Analysis (GSEA) [7] was also performed in order to reveal enriched signatures in our gene sets based on the Molecular Signatures Database (MSigDB) v7.4, and based on publicly available data. Gene sets were ranked by taking the –log10 transform of the p-value multiplied by the Fold Change. Significantly upregulated genes were at the top and significantly downregulated genes were at the bottom of the ranked list. GSEA pre-ranked analysis was then performed using the default settings from the Hallmark v2022 database. The "myeloid

signature" was collected from bibliography. Enrichment was considered significant by the GSEA software for FDR (q-value) <25%.

Reduced Representation Bisulfite Sequencing (RRBS)

Libraries for RRBS were prepared according to a protocol as previously described[8] with minor modifications. Briefly, fresh frozen cell pellets (30,000-130, 000 cells) were lysed by overnight incubation at 55°C with 40 µl lysis buffer (10mM TrisHCl, 5mM EDTA) and 5 µl proteinase K (1 mg/ml; Cat#1245680500, Merck Millipore, Burlington, USA). Proteinase K was then inactivated by incubation with 2 µl 4mM Pefabloc SC (Cat#30827-99-7, Merck Millipore) for 1 h at RT. From each sample 26 µl were cut with 1µl HaeIII (10 U/µl; Cat#R0108T, NEB, Ipswich, USA) overnight at 37°C, followed by A-tailing with Klenow fragment exo- (Cat#M0212M, NEB) and ligation of sample-specific sequencing adaptors using T4-ligase (Cat#M0202M, NEB). After bisulfite conversion with the EZ-DNA methylation Gold kit (Cat#D5005, Zymo research, Irvine, USA) samples were PCR amplified for 15-17 cycles and then purified with AMPure XP beads (Cat#A63881, Beckham Coulter, Brea, USA). NGS libraries were then sequenced for ca. 30 - 70 mio 100 bp single reads on an Illumina HiSeq 2500 machine.

DNA methylation analysis pipeline

Raw reads were trimmed with Trim Galore! (v0.6.4) using the options –rrbs, –illumina and the default value for –quality (Phred score: 20). This way, quality trimming is performed first, and adapter trimming is carried in a second round. Further analysis of fastq files was performed with Bismark (v0.23.1) [9] using the Bowtie2[10] dependency in three individual steps, genome preparation of mouse genome (mm10), alignment and methylation information extraction [9,10]. The bismark.cov.gz files produced from the latter step were then used in R with the methylKit package[11] for further analysis, specifically to detect Differentially Methylated Regions (DMRs) [11–13]. Here, the minimum coverage to read was set to 10 while an extra function was performed where it tiles the genome with a window and step size of 1000bp length and summarizes the methylation information [14]. Finally, for a region to be labeled as differentially methylated, its corrected p-value with SLIM method needed to be less than 0.05 and its absolute value of differential methylation level (|differential methylation level|)> 25% [15]. Regions with value of differential methylation level >25% were considered hypermethylated and regions with value <25% were considered hypomethylated. The resulting DMRs were annotated in R using the software package ChIPseeker [16,17]. Hierarchical clustering using default values of hclust and euclidean distance was performed followed by CpG methylation PCA analysis with autoplot[18]. Additionally, a volcano plot and a heatmap using ggplot2 and heatmap.2 tools in R, was built showing

the hypo- and hyper-methylated regions in each sample [19]. Pie plots were also designed using in-build functions of methylkit and ChIPseeker showing the percentage of DMRs overlapping with exon, intron, promoters but also the CpG island annotation [17].

Integrative analysis of RNA-seq and DNA-methylation

A custom script was built in R combining the RNA sequencing and the DNA methylation results. Using 'bedtools closest', DMRs that were found up to 2Mb away from their closest DEG were retrieved [20]. For each case of the lateral analysis, heatmaps were designed showing the expression of DEGs and the methylation of DMRs. Furthermore, to identify the methylated regulatory factors (promoters, enhancers, transcription factors binding sites and CTCF binding site) of DEGs within the distance (2Mb), we constructed a function that designs dotplots giving all of the information. Specifically, biomaRt package was used in order to get access into the Ensembl database and retrieve the regulatory factors of DEGs, while 'bedtools intersect' was needed to get the DMRs that overlap with the bound regions of those regulatory factors [20–22].

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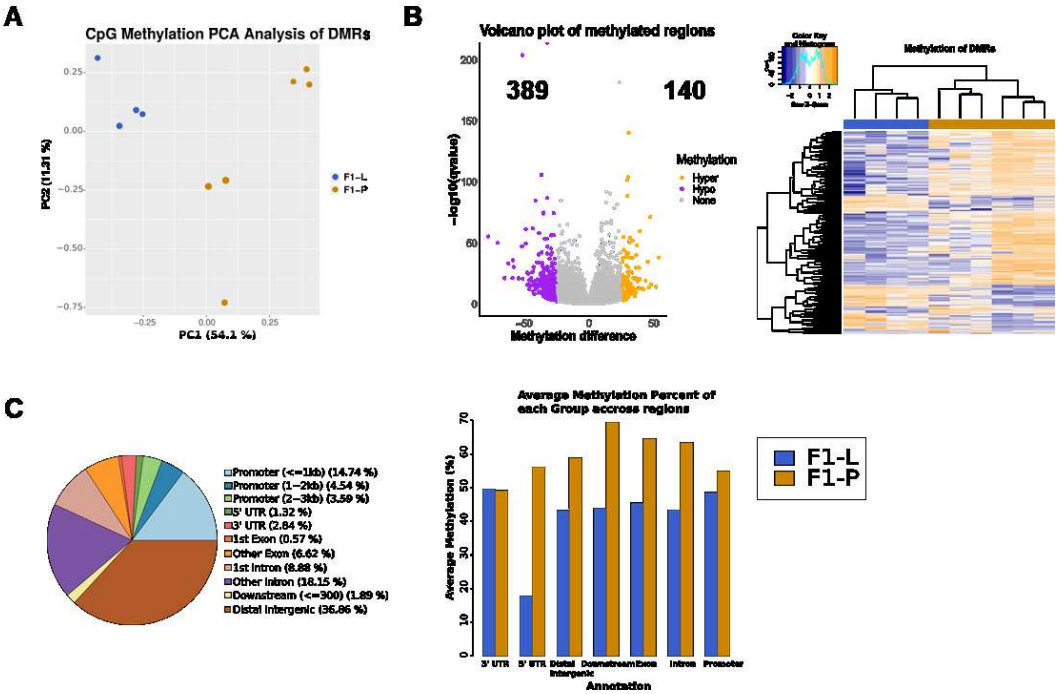
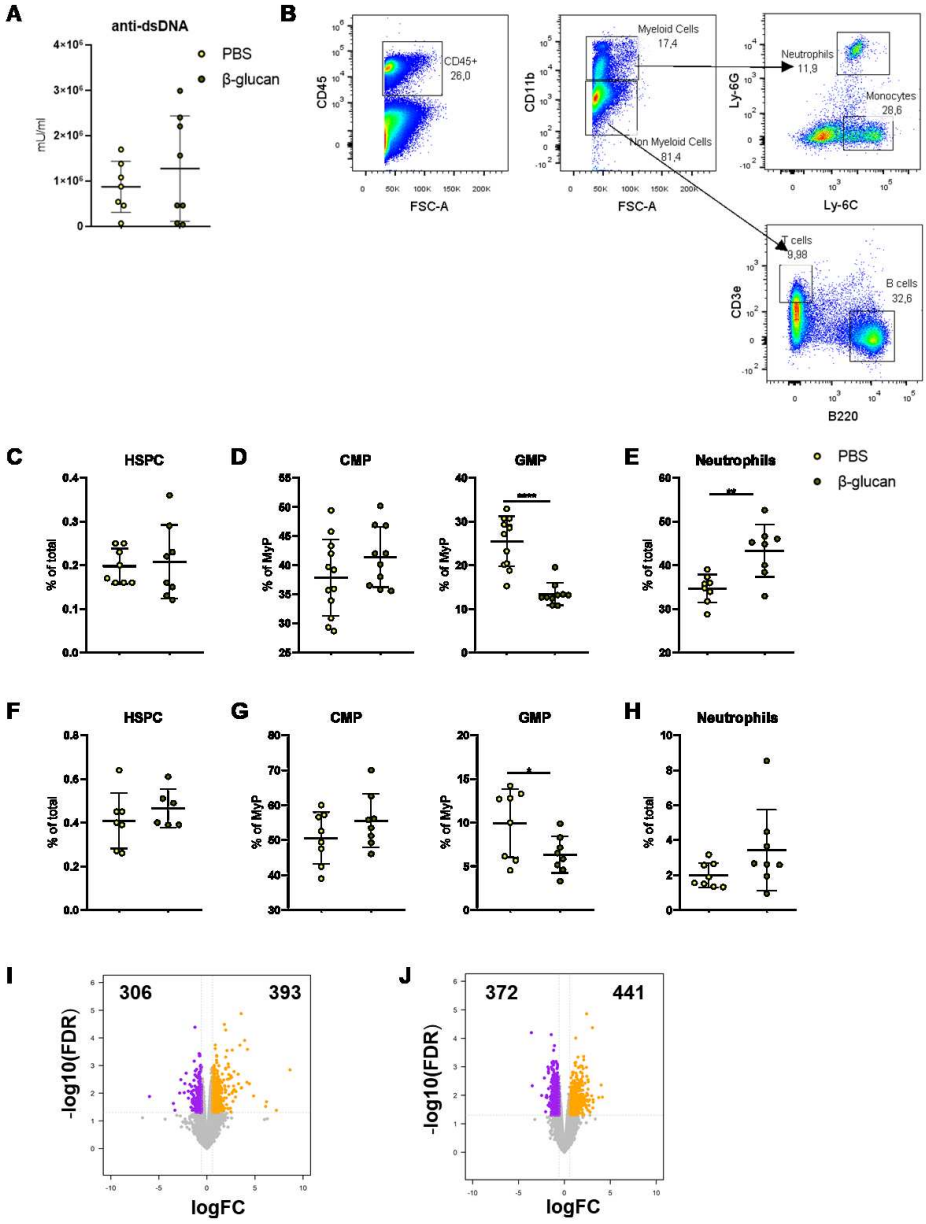
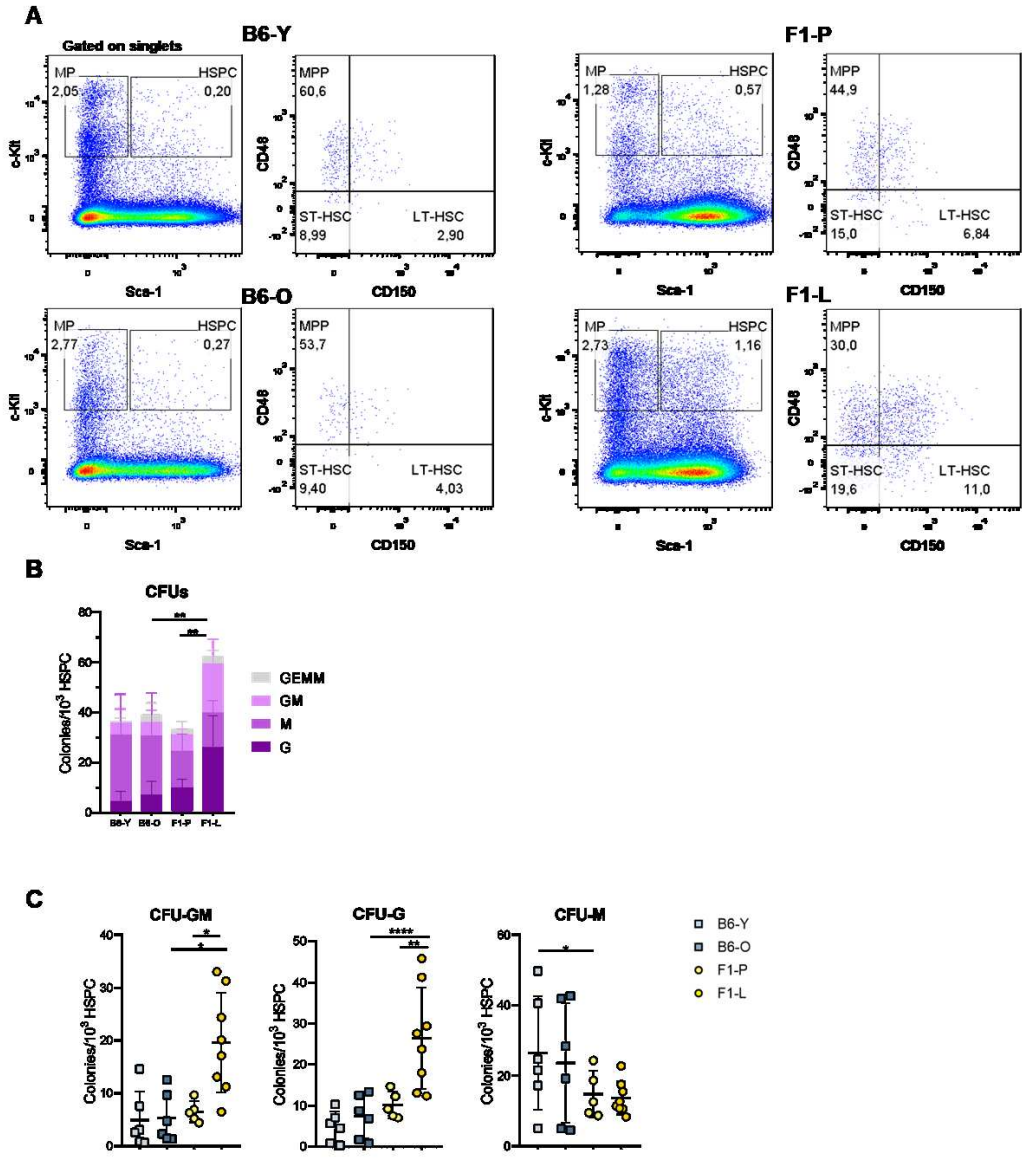


Supplementary Figure 1. (A) Principal component analysis showing the different profile in F1-L from F1-P indicated with blue and orange dots respectively. (B) Volcano plot (left panel) of DMRs between F1-L and F1-P. The horizontal line indicates the threshold of corrected p-value, while the two vertical lines pinpoint the threshold of the absolute value of methylation difference (|differential methylation level|> 25%). Orange, purple and gray dots represent the hyper-, hypo-methylated and the unchanged regions respectively. Heatmap (right panel) of DMRs between F1-L and F1-P. Orange/purple gradient represents the row Z-score of hyper-/hypo-methylation in F1-L compared to F1-P mice. (C) Pie plot (left) visualizing genomic annotation of DMRs in terms of genomic features and barplot (right) showing the average methylation percent of each group across the annotated regions. The y-axis shows the average methylation percent of each annotated region indicated in the x-axis for each group represented by blue (F1-L) and orange (F1-P) colors.

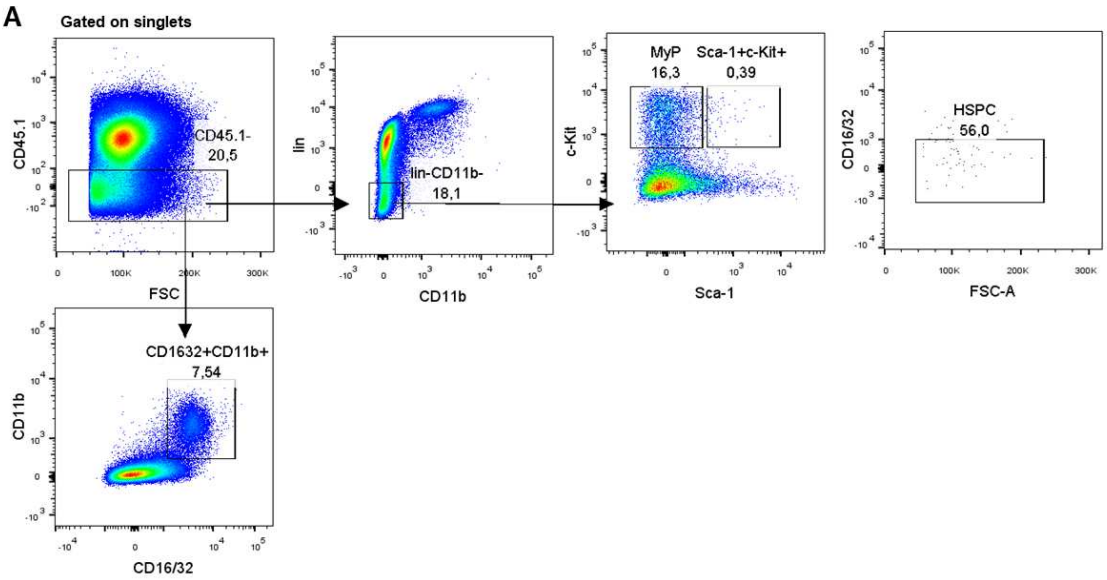


Supplementary Figure 2. (A) Serum titers of anti-dsDNA antibodies (dilution 1:2000) in PBS- and β-glucan-treated F1-L mice (n=7-8). (B) Representative gating of neutrophils ($CD11b^{+}Ly\text{-}6C^{int}Ly\text{-}6G^{hi}$), monocytes ($CD11b^{+}Ly\text{-}6C^{hi}Ly\text{-}6G^{-}$), T ($CD11b^{-}CD3\text{-}e^{+}$) and B cell ($CD11b^{-}B220^{+}$) in the kidney of β-glucan-treated F1-L mice. Frequency of (C) HSPCs, (D) CMPs, GMPs and (E) neutrophils in the BM of PBS- and β-glucan-treated F1-L mice (****p<0.0001, **p=0.0029). Frequency of (F) HSPCs, (G) CMPs, GMPs and (H) neutrophils in the spleen of PBS- and β-glucan-treated F1-L mice (*p=0.0387). Volcano plot of DEGs between (I) BM-derived HSPCs and (J) spleen-derived HSPCs of 'β-glucan- and PBS-treated' F1-L mice. Significantly up- and down-

regulated genes are colored orange and purple respectively. Gray points indicate genes with no significant difference in expression. Data are represented as mean ± SD.



Supplementary Figure 3. (A) Representative gatings of HSPCs gated on Lin$^-$ cells and their subpopulations LT-HSC, ST-HSC and MPPs in all conditions. (B) Total colonies and their types per 10^3 sorted BM-derived HSPC (**p=0.0051 F1-L vs F1-P; **p=0.0091 F1-L vs B6-O). (C) CFU-G, GFU-GM and CFU-M numbers per 10^3 BM-derived HSPC among the conditions (CFU-G: ****p<0,0001; **p=0,001; CFU-GM: *p=0,0028 vs B6-O; *p=0,0123 vs F1-P; CFU-M *p=0,0476; n=5-8). Data are represented as mean ± SD.



Supplementary Figure 4. (A) Representative gating of CD45.1^{-} cells gated on singlets, CD16/32^{+}CD11b^{+} cells, MyPs and HSPCs in the BM of NBSGW recipients which have received spleen-derived HSPCs from F1-L donors.

Supplementary Table 1. Detailed clinical and serological items for each SLE patient.

Sample ID	Age	Proteinuria	Serum albumin levels	ANA	Level of ANA	anti-DNA	Level anti-dsDNA (not specified)	C3 level	C4 level	Nephritis	NPSLE	Serositis	Arthritis	SLEDAI	Severity pattern	Medication at BMA	overall dose of steroids over the last month	past immunosuppressive meds
Sle1	31	1500	3.1	+	low	+	high positive	79	27	+	-	-	No	12	Severe	Pz (15mg), HCQ (400mg), CYC (4g)	465mg	None
Sle2	54	0	3	+	moderate	+	positive	86	17	-	-	-	Yes	15	Severe	CYC (6g), Pz (15mg), HCQ (400mg)	315 mg	None
Sle3	62	0	4.5	+	moderate	+	low positive	86	18	-	-	-	Yes	5	severe	PZ (20mg)	3935 mg	RTX
Sle4	82	2300	3.5	+	low	-	negative	44	10	+	-	+	Yes	14	Severe	PZ (15mg)	3230 mg	None
Sle5	35	0	3.9	+	high	-	negative	163	14	-	-	-	Yes	4	Moderate	HCQ (200mg)	0 mg	None
Sle6	43	50	NA	+	high	+	high positive	34	3.5	-	-	-	Yes	6	Moderate	Pz (5mg), HCQ (200mg)	150mg	None
Sle9	42	8800	3.5	+	high	+	low positive	69	28	+		+	Yes	15	Severe	Rituximab (1g), CYC (500mg), HCQ (400mg)	5100 mg	None
Sle10	46	0	4.2	+	low	-	negative	83	25	-	-	-	Yes	8	Moderate	HCQ (400mg)	112 mg	None

*Footnote: AZA, Azathioprine; MMF, Mycophenolate Mofetil; RTX, Rituximab; CYC, Cyclophosphamide; PRE, Prednisone; HCQ, Hydroxychloroquine
[1] history of LN, [2] history of NPSLE, [3] history of serositis