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Loss of nuclear myosin 1 causes hemostatic defects and immune dysregulation

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Running heads: Nuclear Myosin 1 regulation of hematopoiesis.

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Data-sharing statement: All raw data are publicly available in open-source databases. Raw metabolomic data are publicly available in the Mendeley database (https://data.mendeley.com/preview/nxzs4dtztg?a=aecce665-2b58-4a98-8328-b70d689c249a). RNA sequencing data were deposited in the Gene Expression Omnibus (GEO) repository under accession number GSE293993.

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The role of cellular metabolism in maintaining stem cells' pluripotency and differentiation has been getting more attention due to a direct link between metabolic state and differentiation potential of cells. We showed previously that Nuclear myosin 1 (NM1) deletion leads to a metabolic switch from oxidative phosphorylation to aerobic glycolysis. Therefore, we asked if NM1 contributes to the cell differentiation of hematopoietic progenitor stem cells to terminal blood cells. By using NM1 wild type (WT), knock-out (KO) and NM1-rescued (KO+NM1) mouse embryonic fibroblasts (MEFs), as well as NM1 WT and KO mice, we found that NM1 deletion alters hematopoiesis-related metabolites and differentially regulates genes involved in platelet activation and immune response. NM1 KO mice show decreased erythropoiesis and thrombopoiesis, resulting in impaired hemostasis. In line with enhanced glycolysis, platelet activation is upregulated in NM1 KO bone marrow and blood. Meanwhile, innate immune responses—requiring oxidative phosphorylation for differentiation—are suppressed. In the spleen, innate immune genes are also downregulated, while adaptive immune genes—especially those linked to T-cell activation and regulatory T cell differentiation—are upregulated, consistent with their reliance on glycolysis.

Nuclear Myosin 1 (NM1) has been shown to directly regulate gene expression by binding to the chromatin at the transcription start site, forming a complex with actin and the polymerase machinery, and later anchoring chromatin remodeling complex B-WICH[1, 2], and histone-acetyl- and histone-methyl-transferases PCAF and Set1 to acetylate and methylate surrounding histones for active transcription. Recently, we showed that NM1 is part of the nutrient-sensing PI3K/Akt/mTOR pathway, forming a positive feedback loop with mTOR. NM1 deletion leads to a suppression of mitochondrial transcription factors TFAM and PGC1α, negatively regulating mitochondrial oxidative phosphorylation and leading to metabolic reprogramming towards aerobic glycolysis associated with cancer cells. [3].

Since NM1 regulates cellular metabolism, we investigated whether its deletion affects pluripotent stem cell differentiation and the function of metabolically dynamic somatic cells. Here, we used

hematopoiesis as a model, as hematopoietic stem cells (HSCs) depend on glycolysis and switch to oxidative phosphorylation during differentiation, while mature blood cells adopt cell-specific metabolic programs. For example, erythrocytes lack mitochondria and rely solely on glycolysis [4], lymphocytes use oxidative phosphorylation in their quiescent state and switch to glycolytic metabolism only upon activation [5], and platelets use both pathways but depend on aerobic glycolysis during activation [6, 7].

We performed Liquid Chromatography–High-Resolution Mass Spectrometry followed by Gene Set Enrichment Analysis (GSEA) on cellular extracts from WT and NM1 KO MEFs to identify specific metabolites affected by the deletion of NM1. We identified 5-methylthioadenosine (MTA) (Supplementary Figure 1A) and adenosine monophosphate (AMP) with flavin mononucleotide (FMN) (Supplementary Figure 1B) significantly changed in NM1 KO cells. MTA, a derivative of adenosine, is a key component of the methionine salvage pathway, inhibiting platelet aggregation via increasing of intracellular cyclic adenosine monophosphate (cAMP) [8, 9] and AMP and FMN were shown to alter platelet activation through cAMP and calcium signaling[10, 11].

Given the role of platelet activation in immune responses and inflammation, we investigated whether NM1 expression affects cytokine and chemokine production. Most tested cytokine and chemokine levels were altered in NM1 KO cells and at least partially restored in KO+NM1 cells suggesting a role for NM1 in immune system functionality. Except for IL-1β and IL-11, all other cytokines tested—IL-1α, IL-3, IFN-β, IL-12p40, IL-23, IL-7, IL-33, GM-CSF, IL-12p70, IL-27, and TSLP—were suppressed in NM1 KO cells and restored in KO+NM1 cells (Figure 1A). Several chemokines (RANTES, Eotaxin, MCP-1, MIP-1β, BLC) followed the same suppression/restoration trend. MIP-3α and KC were elevated in NM1 KO cells, while IP-10, MIP-1α, and LIX were unchanged in the KO but increased upon NM1 rescue. TARC and MDC were downregulated in KO cells but not rescued by NM1 reintroduction (Figure 1B). To develop this further, NM1 WT and NM1 KO mice were used for the subsequent analyses. All animal experiments were

performed after approval by the NYUAD-IACUC (Protocol 20-0004, 23-0009). Measurement of cytokine and chemokine levels in the blood serum shows high variability between samples, and even though there are obvious differences between NM1 WT and KO conditions, the data are mostly not statistically significant (Supplementary Figure 1C and 1D). Next, we isolated RNA from bone marrow, spleen, and peripheral blood of WT and NM1 KO mice for deep sequencing and discovered a significant differential gene expression between samples across all tissues (Supplementary figure 2A). The most expression changes are tissue-specific, with limited overlap (Supplementary Figure 2B), suggesting that some effects of NM1 deletion persist from early hematopoiesis in bone marrow to mature blood cells, while others are shaped by tissue-specific environments or metabolic demands. In agreement, gene ontology (GO) analysis of differentially expressed genes shows overlap in biological processes and pathways affected by NM1 deletion between tissues. In bone marrow, the site of hematopoietic differentiation, key affected pathways include cell adhesion, immune processes, platelet activation, and coagulation (Figure 2A). In blood, GO analysis revealed enrichment in coagulation, hemostasis, and cytoskeleton remodeling (Figure 2B); and in spleen, GO analysis indicated the most significantly dysregulated pathways to include those related to cell cycle, immunoglobulin production, and immunoglobulin-mediated immune responses (Figure 2C).

We next analyzed genes linked to hematopoietic differentiation, platelet activation, and coagulation using STRING analysis, which revealed two main clusters (Supplementary Figure 2C): Cluster I, genes involved in platelet activation and coagulation (e.g., *Col1a1, Col1a2, Vwf, GP5, GP9, Gp1ba, Gp1bb, Itgb3, Itga2b, Pf4, Mmrn1, Cd9*, *Serpine2, Serping1, Thbd, Tfpi, G6b, F2Rl3, F2Rl2, Pros1*); and Cluster II, genes involved in signaling (*Mapk13, Mapk3, Src, Mertk, Ptprj, Kitl, Axl, Gas6, Adyc6, Adyc5, Il1A, Gnas, P2Ry1, Gucy1a3, Gucy1b3*). Importantly, a majority of differentially expressed genes related to “Platelet activation,” “Hematopoietic cell lineage,” and “Blood coagulation” are upregulated in NM1 KO bone marrow (Figure 3A). Similarly, although only ~300 genes were differentially expressed in peripheral

blood, most were upregulated, with “Blood coagulation” and “Platelet activation” genes being the most prominent (Figure 3B). Several key genes, including *Vwf, F2rl2, Serpine2, Pros1, G6b*, platelet glycoproteins (*Gp1bb, Gp5, Gp9, Gp1ba*), integrins (*Itga2b, Itgb3, Itgb1*), and other factors like *Gp6, F5, F10, F13a, Ptgs1, Fermt3, Anxa5, Rasgrp2, Rap1b, Rasgrp1, Actb, Actg1, Mylk* were differentially expressed in blood samples (Figure 3B). Given platelet activation’s critical role in peripheral vascular injury and hemostasis, we measured bleeding time in WT and KO mice (Figure 3C). Despite upregulation of platelet activation genes, NM1 KO mice exhibited significantly prolonged bleeding time, indicating impaired clotting efficiency (Figure 3D). Complete blood count analysis revealed significantly reduced platelet counts, decreased red blood cell count, reduced hematocrit and hemoglobin, and increased mean corpuscular volume, consistent with prior findings [12] while white blood cell counts remained unchanged in KO mice (Figure 3E).

Following the abundance of GO terms associated with the immune system in bone marrow and spleen, we analyzed genes related to the immune response process in bone marrow (Supplementary Figure 3A). The affected genes are involved in the innate immune response and antiviral defense (*Ifitm1*, *Ifitm3*, *Serinc5*, *Oas2, Oas3*, *Zbp1*, *Nlrp1a*, *Nlrp1b*, and *Samhd1*), with *Ifn7* (interferon regulatory factor 7) and *Mavs* (mitochondrial antiviral signaling protein) being the most important. The second group contains genes involved in intracellular signaling and immune regulation (*Src*, *Axl*, *Cd4*, *Hck* , *Prkcq*, *Jak3, Tyrobp*, *Tnfaip8l2*, *Pirb*, *Cd300ld*, and *Lst1)* and third is related to the immune complement system (*Cfd*, *C1s1*, *C1qc*, *C1rlSerping1*, and *Fcna).* Although transcriptomic changes in immune system process genes are less pronounced than for platelet activation genes, a heatmap shows that most are downregulated in NM1 KO bone marrow (Supplementary Figure 3A).

Since many immune cells reside and activate in secondary lymphoid organs, we next analyzed spleen tissues from NM1 WT and KO mice. In contrast to bone marrow, immune system-related genes in the

NM1 KO spleen tissue are predominantly upregulated, with many genes being variable or constant segments of immunoglobulin heavy and light chains, which do not possess intrinsic function (Supplementary Figure 3B). We then generated expression heatmaps based on the role in innate or adaptive immunity. The innate immune cluster contains *Irf7*, *Eif2ak2*, *Herc6*, *Oas3*, *Rsad2*, *Isg20*, *Serinc*, *Ikbke*, *Traf4*, *TifaRiok3*, *Ilrun*, *Mfhas1*, *Zcchc3*, *Ccl8*, *Mst1r*, *F2rl1*, *Slamf7*, *Mcoln2*, *Akirin2*, *Tnfrsf14*, *Cd24a*, *Prdm1*, *Zap70*, *Jak3* genes (Supplementary Figure 3C). The adaptive immune gene cluster consists of genes regulating B and T cell function, with most genes associated with T cell development, signaling and activation (*Themis*, *Foxp3*, *Prdm1*, *Fas*, *Jak3*, *Sema4a*, *Cd4*, *Cd8a*, *Cd8b1*, *Cd247*, *Itk*, *C3*, *Ctla4*, *Alcam*, *Slamf7*, *Irf4*, *Zap70*, *Tnfsrf14*) (Supplementary Figure 3D). Furthermore, expression patterns suggest expansion of subpopulations of Cd4+ Foxp3+ CD25+, Cd8+ Foxp3+ CD25+, CD8+ CD122+ PD-1+ and CD8+ CTLA4+ regulatory T cells (Tregs).

Interestingly, while innate immune genes are generally downregulated, with overlap between bone marrow and spleen, adaptive immune genes are largely upregulated, implying a possible antagonistic role of NM1 in regulating innate versus adaptive immune responses.

Taken together, transcriptomic, and functional analyses reveal that NM1 contributes to global body homeostasis by regulating the differentiation and activity of specific hematopoietic cell types. We hypothesize that NM1 affects the destiny of these cells by transcriptional regulation of their metabolic status.

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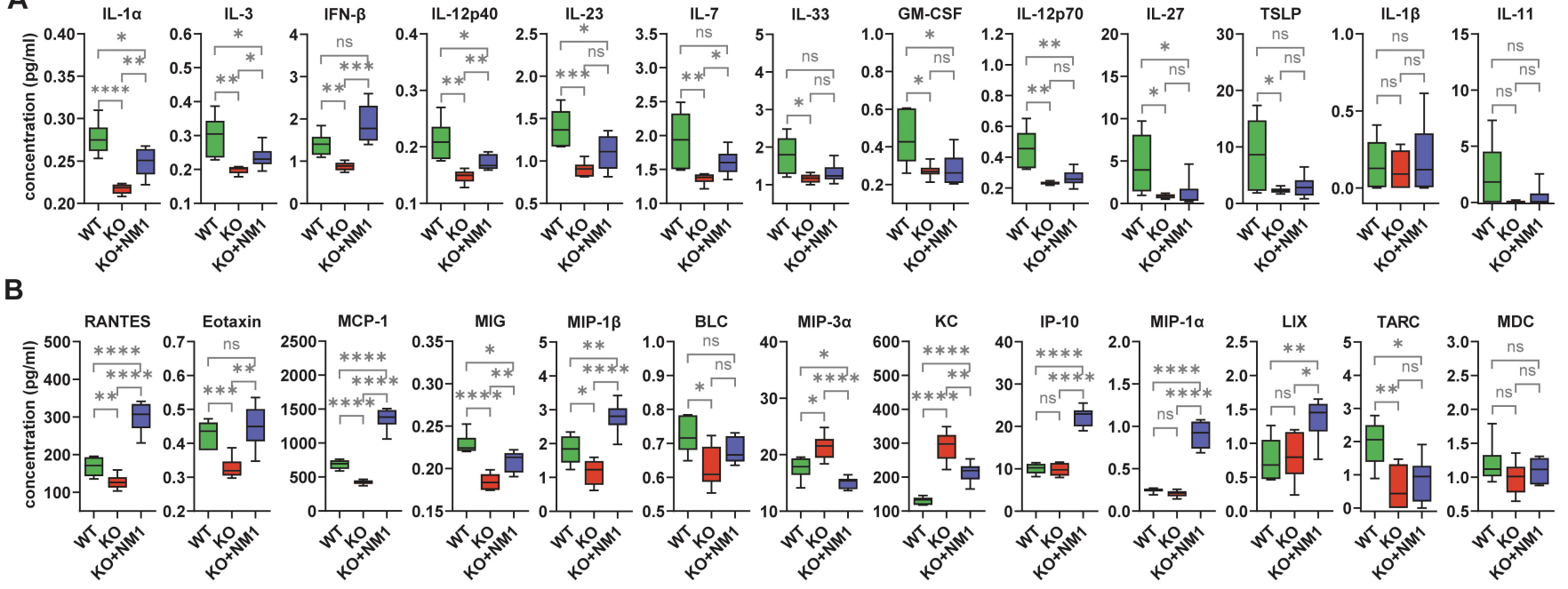
Figure legends

Figure 1. NM1 deletion leads to changes in cytokine/chemokine profile. (A) List of analyzed cytokines in NM1 WT, NM1 KO and rescued NM1 KO+NM1 cells. ns $P > 0.05$, * $P \leq 0.05$, ** $P \leq 0.001$, *** $P \leq 0.001$, **** $P \leq 0.0001$. **(B)** List of analyzed chemokines in NM1 WT, NM1 KO, and rescued NM1 KO+NM1 cells. ns $P > 0.05$, * $P \leq 0.05$, ** $P \leq 0.001$, *** $P \leq 0.001$, **** $P \leq 0.0001$.

Figure 1. NM1 deletion leads to changes of gene expression in hematopoietic tissues. (A) Gene ontology analysis based on all differentially expressed genes between experimental conditions in bone marrow shows biological process-, cellular component-, and KEGG pathway-associated gene ontology terms plotted in descending order based on their significance. **(B)** Gene ontology analysis based on all differentially expressed genes between experimental conditions in blood shows biological process-, cellular component-, and KEGG pathway-associated gene ontology terms plotted in descending order based on their significance. **(C)** Gene ontology analysis based on all differentially expressed genes between experimental conditions in the spleen shows biological process-, cellular component-, and KEGG pathway-associated gene ontology terms plotted in descending order based on their significance.

Figure 3. NM1 deficiency leads to hematopoiesis differentiation and hemostasis defects in mice. (A) Heatmap of all differentially expressed genes between NM1 WT and KO bone marrow samples associated with Platelet activation GO terms used in String analysis. **(B)** Heatmap of all differentially expressed genes between NM1 WT and KO blood samples associated with the GO terms “Blood coagulation” and “Platelet activation”. **(C)** Schematic diagram illustrating the experimental procedure, where mice undergo a tail cut for bleeding time (BT) measurement. Following this, whole blood is collected via cardiac puncture for subsequent complete blood count analysis. **(D)** Bleeding time (BT)

analysis between NM1 WT and KO mice. (n = 5 WT, 9 KO) The two-tailed Mann-Whitney U test was used for statistical analysis. * P≤0.05 **(E)** CBC profiles in WT and NM1 KO mice. Violin plots show platelet count (PTL), white blood cell count (WBC), red blood cell count (RBC), hematocrit (HCT), hemoglobin (HGB), and mean corpuscular volume of red blood cells (MCV) for both groups (n = 3 WT, 4 KO). The two-tailed Mann-Whitney U test was used for statistical analysis. * P≤0.05, ** P≤0.001, *** P≤0.001, **** P≤0.0001.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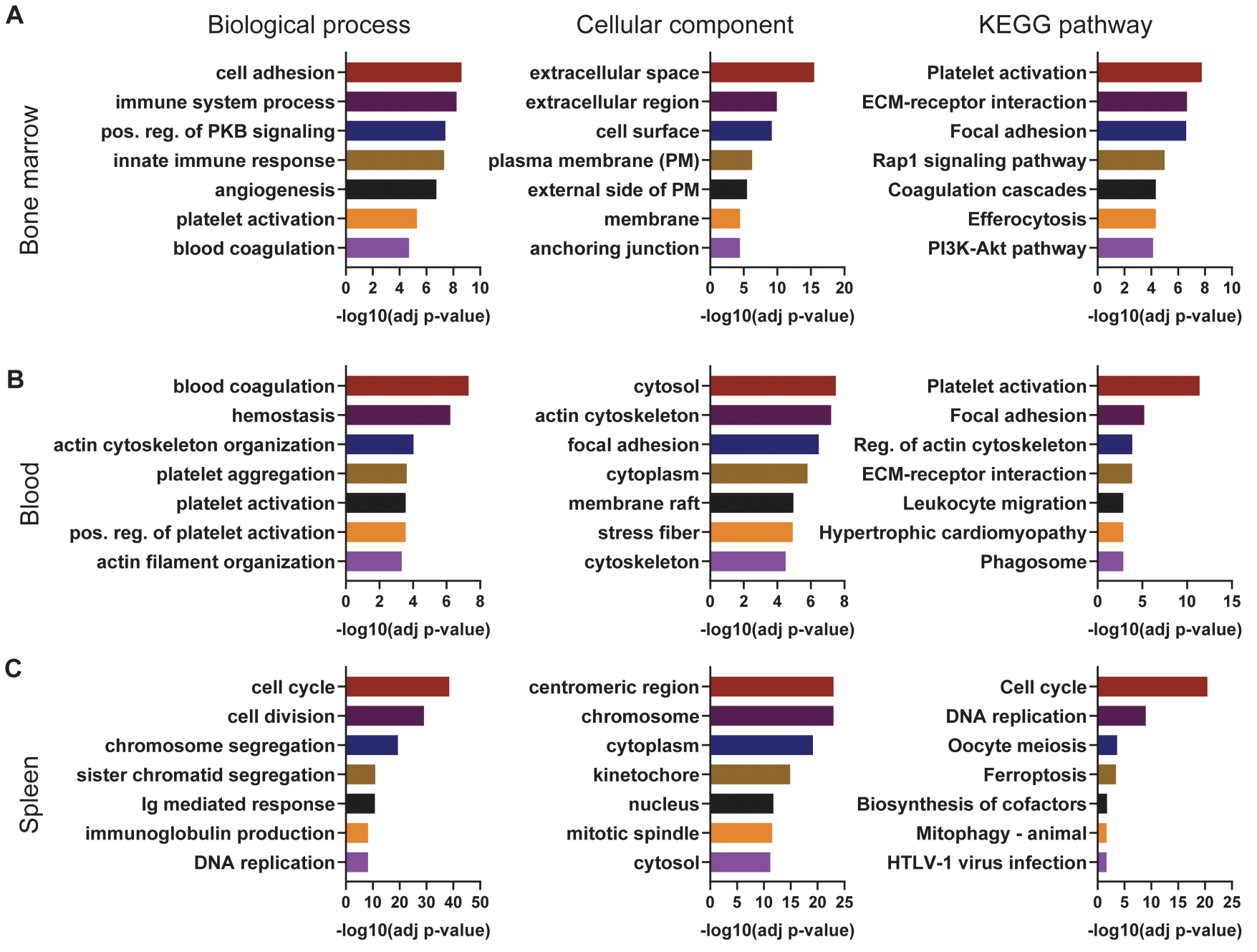
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external side of PM
membrane
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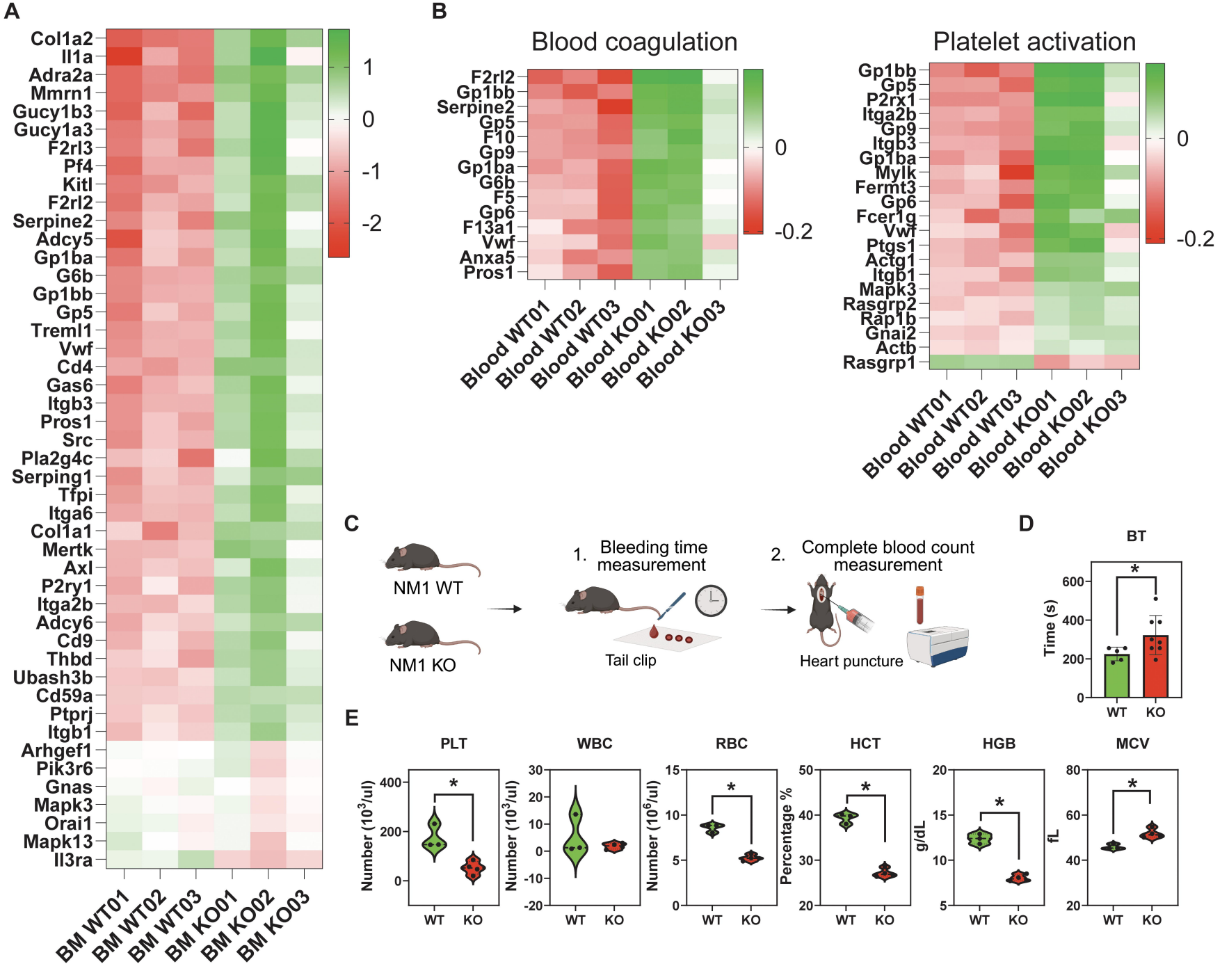
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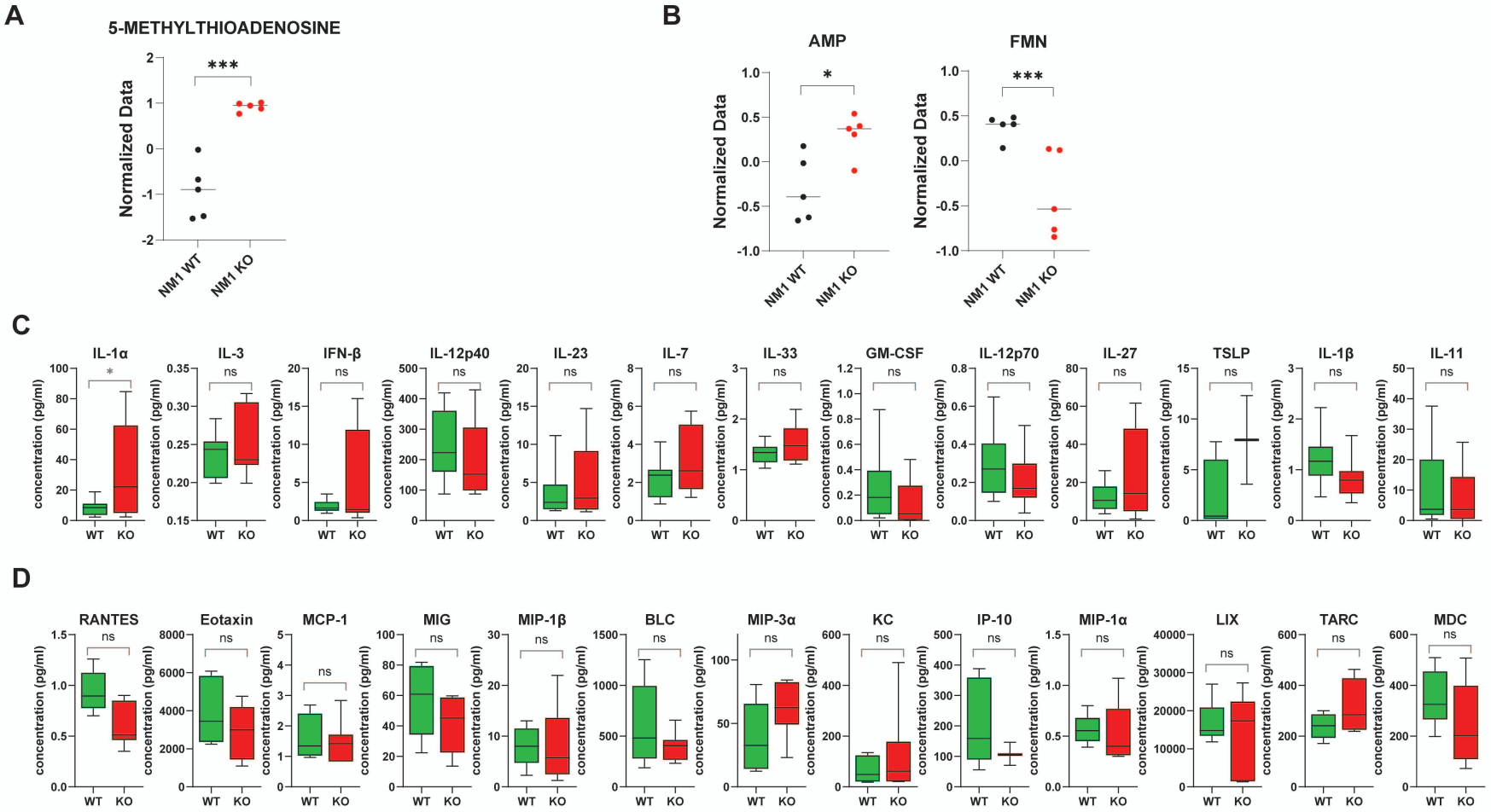
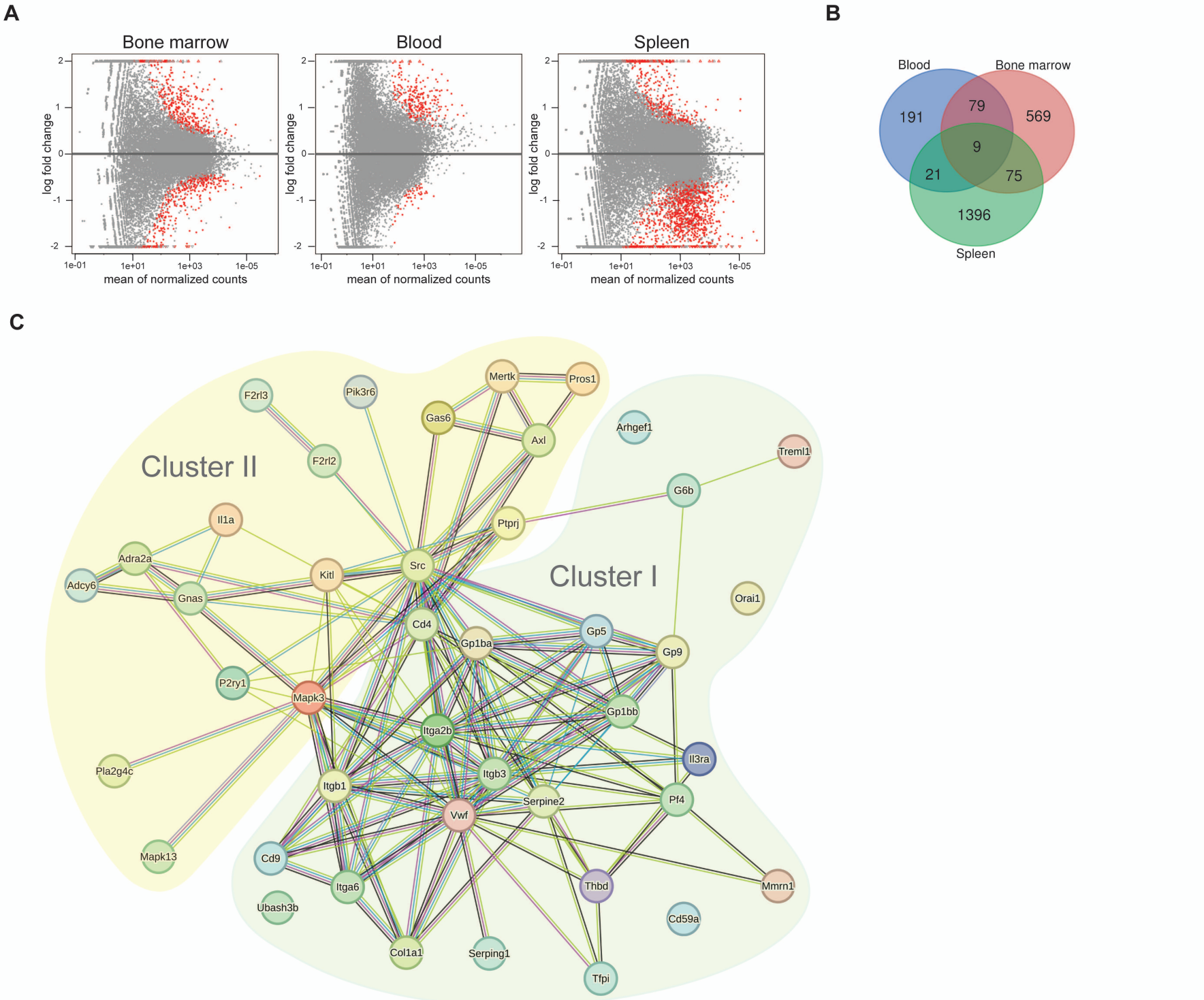
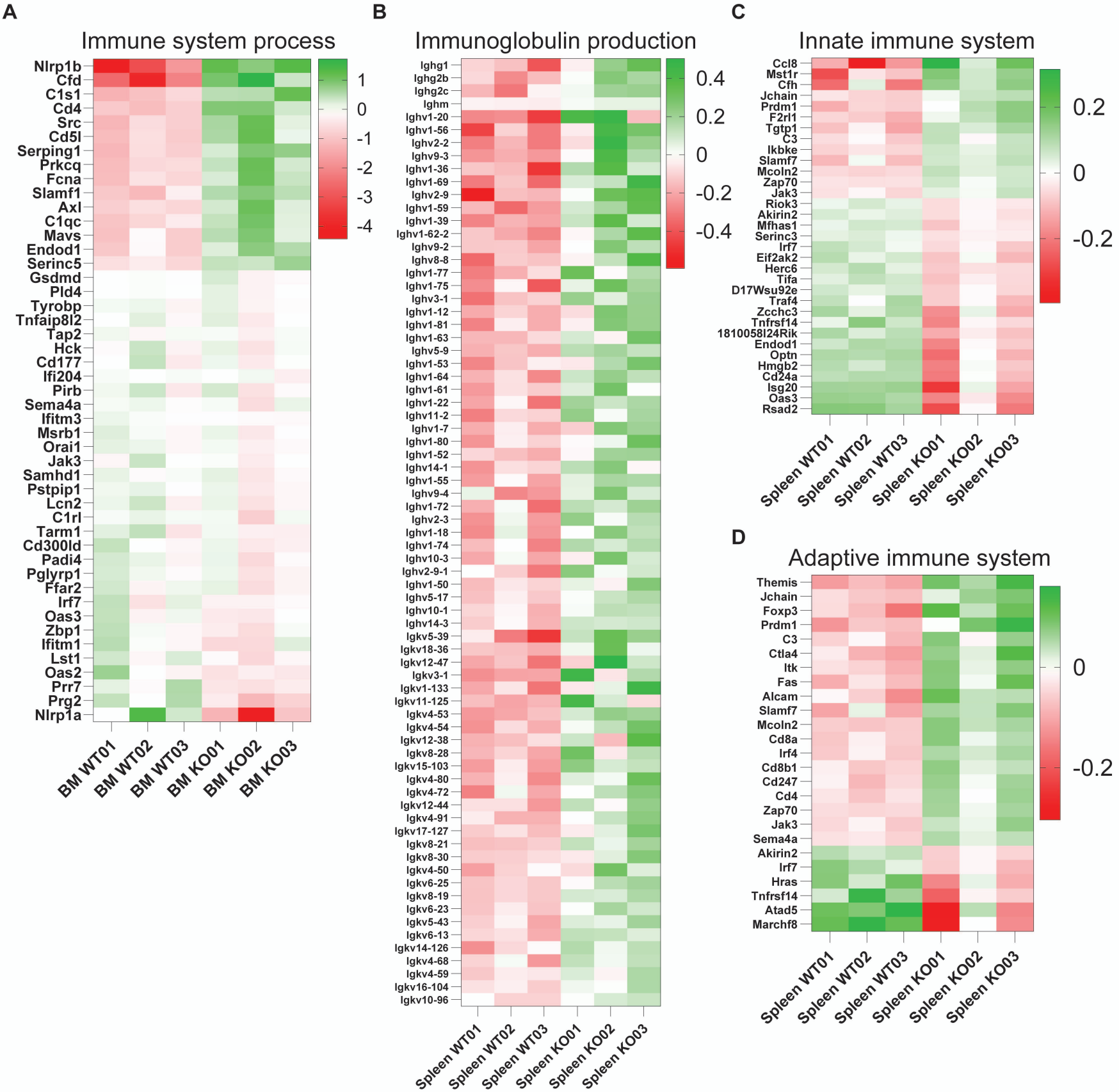


Supplementary figure 1. NM1 deletion leads to changes in hematopoietic signature metabolites and cytokine/chemokine profiles. (A) Metabolomic profile of 5-methylthioadenosine (MTA) across experimental samples as detected by positive ionization. *** P≤0.001 (B) Metabolomic profile of AMP and FMN across experimental samples as detected by negative ionization. * P≤0.05, *** P≤0.001 (C) List of analyzed cytokines in NM1 WT and NM1 KO serum samples. ns P > 0.05, * P ≤0.05. (D) List of analyzed chemokines in NM1 WT and NM1 KO serum samples. ns P > 0.05, * P≤0.05.



Supplementary figure 2. (A) MA plot visualization of the differences in gene expression between experimental conditions as a function of log fold change versus the mean of normalized counts. Each dot represents a single gene expression profile with only red-marked genes to be significantly differentially expressed. (B) Venn diagram showing the intersection in all differentially expressed genes between hematopoietic tissues. (C) String analysis diagram of all differentially expressed bone marrow genes associated with a KEGG GO term “Platelet activation”, a Biological process GO term “Platelet activation”, KEGG GO term “Haemopoietic cell lineage”, and Biological GO term “Blood coagulation”.



Supplementary figure 3. Gene expression analysis of genes associated with the innate and adaptive immune system in the bone marrow and spleen. (A) Heatmap of all differentially expressed genes between NM1 WT and KO bone marrow samples associated with Innate immune system GO term. (B) Heatmap of all differentially expressed genes between NM1 WT and KO spleen samples associated with Immunoglobulin production. (C) Heatmap of all differentially expressed genes between NM1 WT and KO spleen samples associated with the innate immune system. (D) Heatmap of all differentially expressed genes between NM1 WT and KO spleen samples associated with the adaptive immune system.