SUPPLEMENTAL MATERIAL

Endothelial METTL3 (methyltransferase-like 3) Inhibits Fibrinolysis by Promoting PAI-1 Expression through Enhancing JUN m^{6}A Modification

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Major Resources Table

In order to allow validation and replication of experiments, all essential research materials listed in the Methods should be included in the Major Resources Table below. Authors are encouraged to use public repositories for protocols, data, code, and other materials and provide persistent identifiers and/or links to repositories when available. Authors may add or delete rows as needed.

Animals (in vivo studies)

Species	Vendor or Source	Background Strain	Sex	Persistent ID / URL
Mouse	Laboratory Animal Center, Daping Hospital of Army Medical University	C57BL/6J	Male and female	

Genetically Modified Animals

	Species	Vendor or Source	Background Strain	Other Information	Persistent ID / URL
Parent - Male	$Tie2^{Cre}$ mice	The Jackson Laboratory	C57BL/6J		
Parent - Female	*Mettl3* ^{floxed} mice	Chinese Academy of Sciences	C57BL/6J		

Antibodies

Target antigen	Vendor or Source	Catalog #	Working concentration	Lot # (preferred but not required)	Persistent ID / URL
METTL3	ABclonal	A8370	1:2000		
PAI-1	Abcam	ab182973	1:1000		
JUN	Cell Signaling Technology	9165S	1:500		
YTHDF1	Proteintech	17479-1-AP	1:4000		
GAPDH	Proteintech	10494-1-AP	1:10000		
Flag	Proteintech	20543-1-AP	1:2000		
m^6A	Abcam	ab151230	2μg/mL		
Anti-rabbit IgG HRP	santa cruz biotechmology	sc-2357	1:5000		
Anti-mouse IgG HRP	Proteintech	SA00001-1	1:5000		
Anti-rabbit IgG (Cy3)	Abcam	ab6939	1:500		
Mouse IgG	Abcam	Ab37355	1:1000		
Anti-fibrin（clone 59D8）	Merck	MABS2155	1ug/ml		
CD31	Biolegend	102502	5ug/ml		
ICAM-2	Biolegend	105602	5ug/ml		

DNA/cDNA Clones

Clone Name	Sequence	Source / Repository	Persistent ID / URL

METTL3	gattacaaggatgacgatgacaagtcggacacgtggagctctatccaggcccacaa gaagcagctggactctctgcgggagaggctgcagcggaggcggaagcaggactc ggggcacttggatctacggaatccagaggcagcattgtctccaaccttccgtagtgac agcccagtgcctactgcacccacctctggtggccctaagcccagcacagcttcagca gttcctgaattagctacagatcctgagttagagaagaagttgctacaccacctctctgat ctggccttaacattgcccactgatgctgtgtccatctgtcttgccatctccacgccagatg ctcctgccactcaagatggggtagaaagcctcctgcagaagtttgcagctcaggagtt gattgaggtaaagcgaggtctcctacaagatgatgcacatcctactcttgtaacctatg ctgaccattccaagctctctgccatgatgggtgctgtggcagaaaagaagggccctg gggaggtagcagggactgtcacagggcagaagcggcgtgcagaacaggactcg actacagtagctgcctttgccagttcgttagtctctggtctgaactcttcagcatcggaac cagcaaaggagccagccaagaaatcaaggaaacatgctgcctcagatgttgatctg gagatagagagccttctgaaccaacagtccactaaggaacaacagagcaagaag gtcagtcaggagatcctagagctattaaatactacaacagccaaggaacaatccatt gttgaaaaatttcgctctcgaggtcgggcccaagtgcaagaattctgtgactatggaac caaggaggagtgcatgaaagccagtgatgctgatcgaccctgtcgcaagctgcactt cagacgaattatcaataaacacactgatgagtctttaggtgactgctctttccttaataca tgtttccacatggatacctgtaaatacgtacattacgagattgatgcttgcatggattctg aggcccctggcagcaaagaccacacgccaagccaggagcttgctcttacacagag tgtcggaggtgattccagtgcagaccgactcttcccacctcagtggatctgttgtgatat ccgctacctggacgtcagtatcttgggcaagtttgcagttgtgatggctgacccaccctg ggatattcacatggaactgccctatgggaccctgacagatgatgagatgcgcaggct caacatacccgtactacaggatgatggctttctcttcctctgggtcacaggcagggcca tggagttggggagagaatgtctaaatctctgggggtatgaacgggtagatgaaattatt tgggtgaagacaaatcaactgcaacgcatcattcggacaggccgtacaggtcactg gttgaaccatgggaaggaacactgcttggttggtgtcaaaggaaatccccaaggcttc aaccagggtctggattgtgatgtgatcgtagctgaggttcgttccaccagtcataaacc agatgaaatctatggcatgattgaaagactatctcctggcactcgcaagattgagttatt tggacgaccacacaatgtgcaacccaactggatcacccttggaaaccaactggatg ggatccacctactagacccagatgtggttgcacggttcaagcaaaggtacccagatg gtatcatctctaaacctaagaatttatag		
JUN	gattacaaggatgacgacgataagactgcaaagatggaaacgaccttctatgacga tgccctcaacgcctcgttcctcccgtccgagagcggaccttatggctacagtaacccc aagatcctgaaacagagcatgaccctgaacctggccgacccagtggggagcctga agccgcacctccgcgccaagaactcggacctcctcacctcgcccgacgtggggctg ctcaagctggcgtcgcccgagctggagcgcctgataatccagtccagcaacgggca catcaccaccacgccgacccccacccagttcctgtgccccaagaacgtgacagatg agcaggagggcttcgccgagggcttcgtgcgcgccctggccgaactgcacagcca gaacacgctgcccagcgtcacgtcggcggcgcagccggtcaacggggcaggcat ggtggctcccgcggtagcctcggtggcaggggcagcggcagcggcggcttcagc gccagcctgcacagcgagccgccggtctacgcaaacctcagcaacttcaacccag gcgcgctgagcagcggcggcggggcgccctcctacggcgcggccggcctggccttt cccgcgcaaccccagcagcagcagcagccgccgcaccacctgccccagcagatg cccgtgcagcacccgcggctgcaggccctgaaggaggagcctcagacagtgccc gagatgcccggcgagacaccgcccctgtcccccatcgacatggagtcccaggagc ggatcaaggcggagaggaagcgcatgaggaaccgcatcgctgcctccaagtgcc gaaaaaggaagctggagagaatcgcccggctggaggaaaaagtgaaaaccttga aagctcagaactcggagctggcgtccacggccaacatgctcagggaacaggtggc acagcttaaacagaaagtcatgaaccacgttaacagtgggtgccaactcatgctaac gcagcagttgcaaacattttga		
PAI-1	gattacaaggatgacgacgataagcagatgtctccagccctcacctgcctagtcctgg gcctggcccttgtctttggtgaagggtctgctgtgcaccatcccccatcctacgtggccc acctggcctcagacttcggggtgagggtgtttcagcaggtggcgcaggcctccaagg accgcaacgtggttttctcaccctatggggtggcctcggtgttggccatgctccagctga caacaggaggagaaacccagcagcagattcaagcagctatgggattcaagattga tgacaagggcatggcccccgccctccggcatctgtacaaggagctcatggggccat		

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Cultured Cells

Name	Vendor or Source	Sex (F, M, or unknown)	Persistent ID / URL
HUVEC	Cell Bank, Chinese Academy of Sciences	unknown	
HEK293T	Cell Bank, Chinese Academy of Sciences	unknown	

shRNA oligonucleotide sequences

Gene	Forward	Reverse
Homo sapiens		
METTL3	CCGGGCAAGTATGTTCACTATGAAACTCGA GTTTCATAGTGAACATACTTGCTTTTTG	AATTCAAAAAGCAAGTATGTTCACTATGAAA CTCGAGTTTCATAGTGAACATACTTGC
YTHDF1	CCGGCCCGAAAGAGTTTGAGTGGAACTCG AGTTCCACTCAAACTCTTTCGGGTTTTTG	AATTCAAAAACCCGAAAGAGTTTGAGTGGA ACTCGAGTTCCACTCAAACTCTTTCGGG
JUN	CCGGCGCAAACCTCAGCAACTTCAACTCG AG TTGAAGTTGCTGAGGTTTGCGTTTTTG	AATTCAAAACGCAAACCTCAGCAACTTCAA CTCGAGTTGAAGTTGCTGAGGTTTGCG
PAI-1	CCGGTCTCTGCCCTCACCAACATTCCTCGA GGAATGTTGGTGAGGGCAGAGATTTTTG	AATTCAAAATCTCTGCCCTCACCAACATTC CTCGAGGAATGTTGGTGAGGGCAGAGA
scramble	CCGGCCTAAGGTTAAGTCGCCCTCGCTCG AGCGAGGGCGACTTAACCTTAGGTTTTTG	AATTCAAAAACCTAAGGTTAAGTCGCCCTC GCTCGAGCGAGGGCGACTTAACCTTAGG

qPCR primer information

Gene	Forward	Reverse
Homo sapiens		
METTL3	AGTCCACTAAGGAACAACAGAG	ATTCTGTGACTATGGAACCAAG
YTHDF1	TTCGTTACATCAGAAGGATACA	GTAATAGCTGGACAGGTAGGG
JUN	CTGTTCTATGACTGCAAAGATG	GGGTTACTGTAGCCATAAGGT
PAI-1	AGGGCTTCATGCCCCACTTCTTCA	AGTAGAGGGCATTCACCAGCACCA
TFPI	ATTTATATATGGGGGATGTGAA	CCTGGTAATATAACCTCGACAT
t-PA	GATGATATACCAGCAACATCAG	AACTTTTGACAGGCACTGAG
u-PA	TAAGTCAAAAACCTGCTATGAG	GTACGTTTGCTGAAGGACAG
ITGA2	TTCCA AATGTTACTGAGATGAA	TGTAATACTGATTCCCACATTG
SLC7A11	GGAAGAGATTCAAGTATTACGC	CATGGATATACATATTGCAAGG
SERPINE2	GCATTACTGACATGTTTGATTC	ACTGACTTCAATTTTTGCTTTT

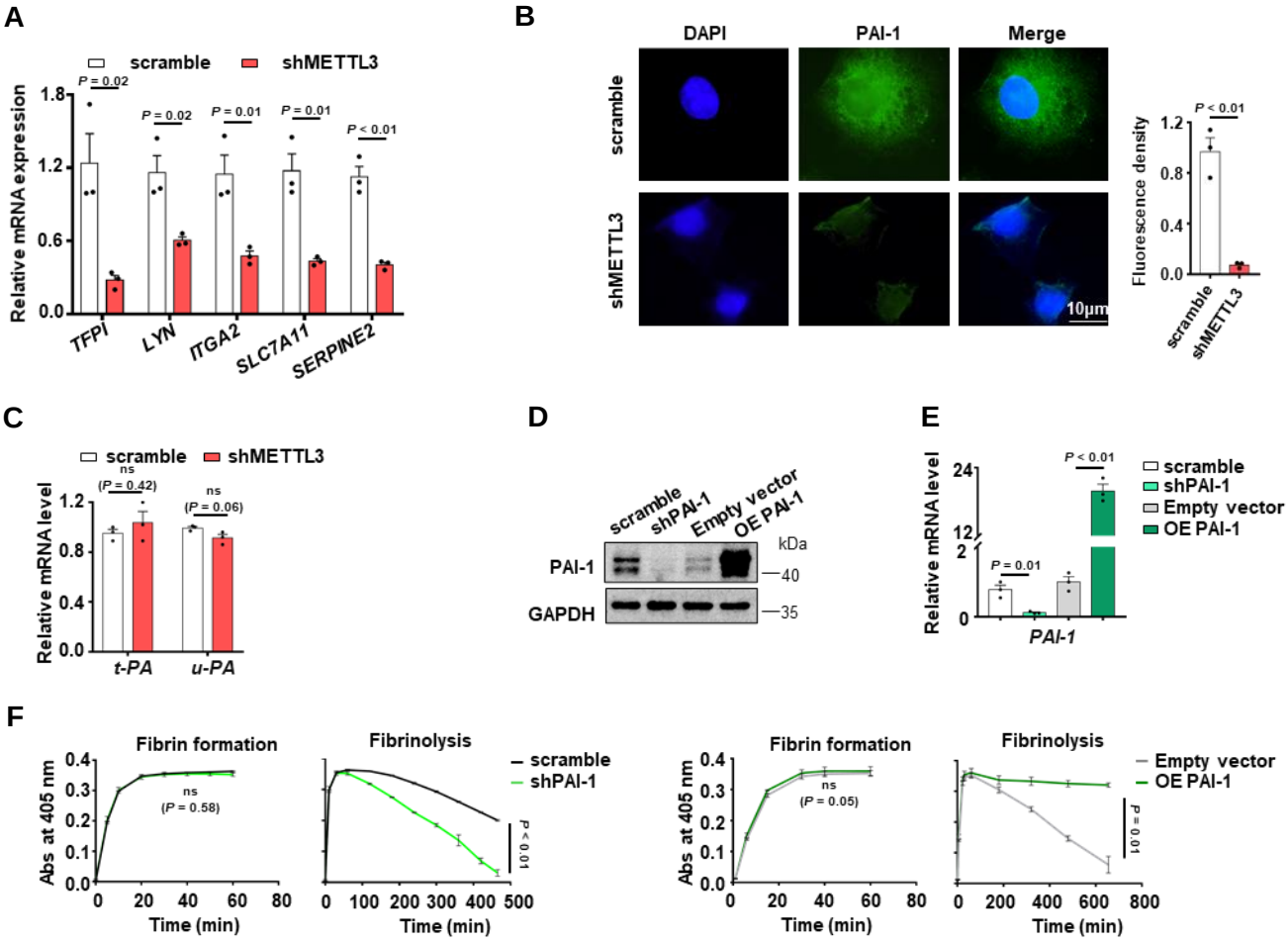
UPP1	TCATAAAGCTGCTGTACTATGC	CTGCTCTGTTATGACCACAGT
EMP1	TGGAAAAACTGTACCAACATTA	GCAATGACACAGAAGATGATAG
LYN	ACGATGGAGTAGATTTGAAGAC	GTTCCTCTGGATCTTTAGTTTG
YTHDF2	GGAAACAAAGTACAAAATGGAT	GAGGGACTGTAGTAACTGGGTA
GAPDH	TCTCCTCTGACTTCAACAGCGACA	CCCTGTTGCTGTAGCCAAATTCGT
Mouse		
Mettl3	TCACTATGAAATTGATGCTTGT	GATATCACAACAGATCCACTGA
Jun	AAGATGGAAACGACCTTCTAC	GTCATGCTCTGTTTTAGGATCT
Pai-1	ACATCTTGGATGCTGAACTC	CTTCAGTCTCCAGAGAGAACTT
Gapdh	CGACTTCAACAGCAACTCCCACTCTTCC	TGGGTGGTCCAGGGTTTCTTACTCCTT

Me-RIP-qPCR primers

Gene	Forward	Reverse
Homo sapiens		
JUN m^{6}A	GGGTTACTGTAGCCATAAGGT	CTGTTCTATGACTGCAAAGATG
GAPDH m^{6}A	TCAAGGCTGAGAACGGGAAG	GGACTCCACGACGTACTCAG

Primers used for ChIP

Gene	Forward	Reverse
Homo sapiens		
PAI-1	CTGAGAACTTCAGGTAGGAGAA	GGAAAAGAAAATAGAGGAATAGC
ACTB	CCTCATGGCCTTGTCACACGAG	GCCCTTTCTCACTGGTTCTCT



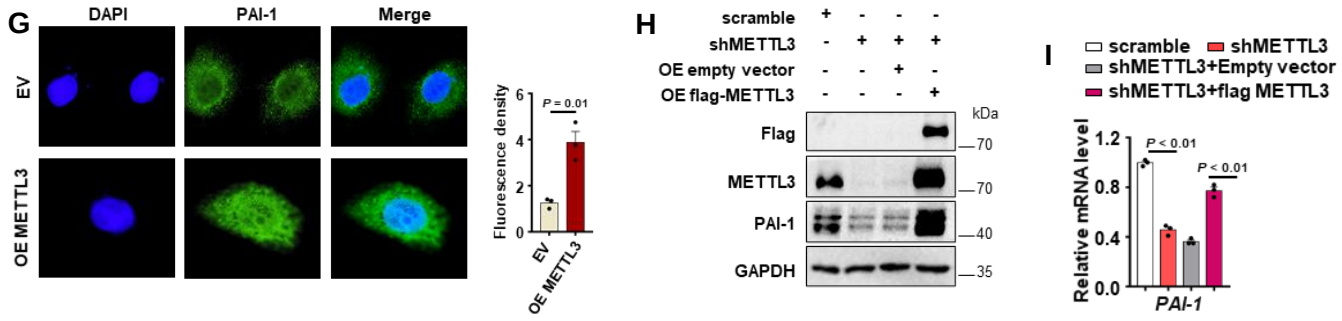


Figure Ⅰ. METTL3 impaires fibrinolytic ability by elevating PAI-1 levels.

(A) qPCR analysis of *TFPI*、*LYN*、*ITGA2*、*SLC7A11*、*SERPINE2* mRNA expression in shMETTL3 HUVECs and control cells (n=3, data are mean ± SEM). (B) Immunofluorescence measured the expression of PAI-1 in control and shMETTL3 HUVECs (n=3, data are mean ± SEM). (C) qPCR analysis of *t-PA* and *u-PA* mRNA expression in shMETTL3 HUVECs and control cells (n=3, data are mean ± SEM). (D-E) Western blot and qPCR detected the expression of PAI-1 in PAI-1 knockdown and overexpressed HUVECs (n=3, data are mean ± SEM). (F) Fibrin formation and fibrinolysis were shown in shPAI-1 HUVECs and PAI-1 overexpressed HUVECs (n=3, data are mean ± SEM). (G) Immunofluorescence detected the expression of PAI-1 in control and OE METTL3 HUVECs (n=3, data are mean ± SEM). (H-I) Western blot and qPCR were conducted to detect the protein (H) and mRNA (I) level of PAI-1 in HUVECs after METTL3 intervention (n=3, data are mean ± SEM). OE: overexpression; EV: Empty vector.

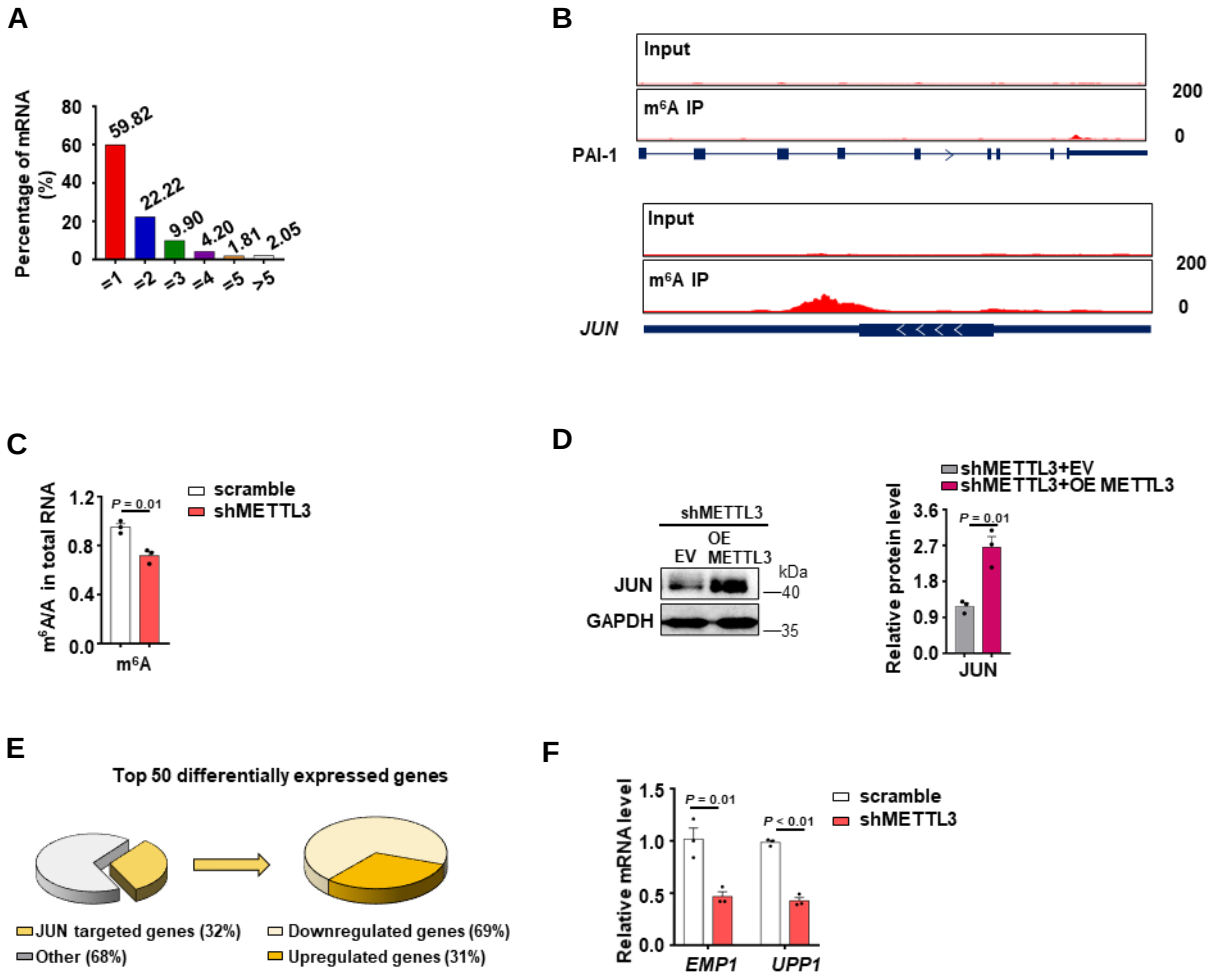


Figure Ⅱ. METTL3 mediates *JUN* mRNA m⁶A modification.

(A) Percentage of m^{6}A-methylated mRNAs with different numbers of m^{6}A peaks. (B) m^{6}A-seq detected the abundance of m^{6}A on *PAI-1* and *JUN* mRNA. (C) m^{6}A level was qualitative using an antibody-mediated m^{6}A capture assay in shMETTL3 HUVECs (n=3, data are mean ± SEM). (D) Western blot along with the quantification in METTL3 rescued HUVECs (n=3, data are mean ± SEM). (E) Pie chart depicted the targets of JUN transcription factor among the top 50 differentially expressed genes in RNA-Seq (fold change >2 and adjusted *p*-value <0.05). (F) qPCR measured the mRNA expression of *UPP1* and *EMP1* (n=3, data are mean ± SEM). OE: overexpression, EV: empty vector.

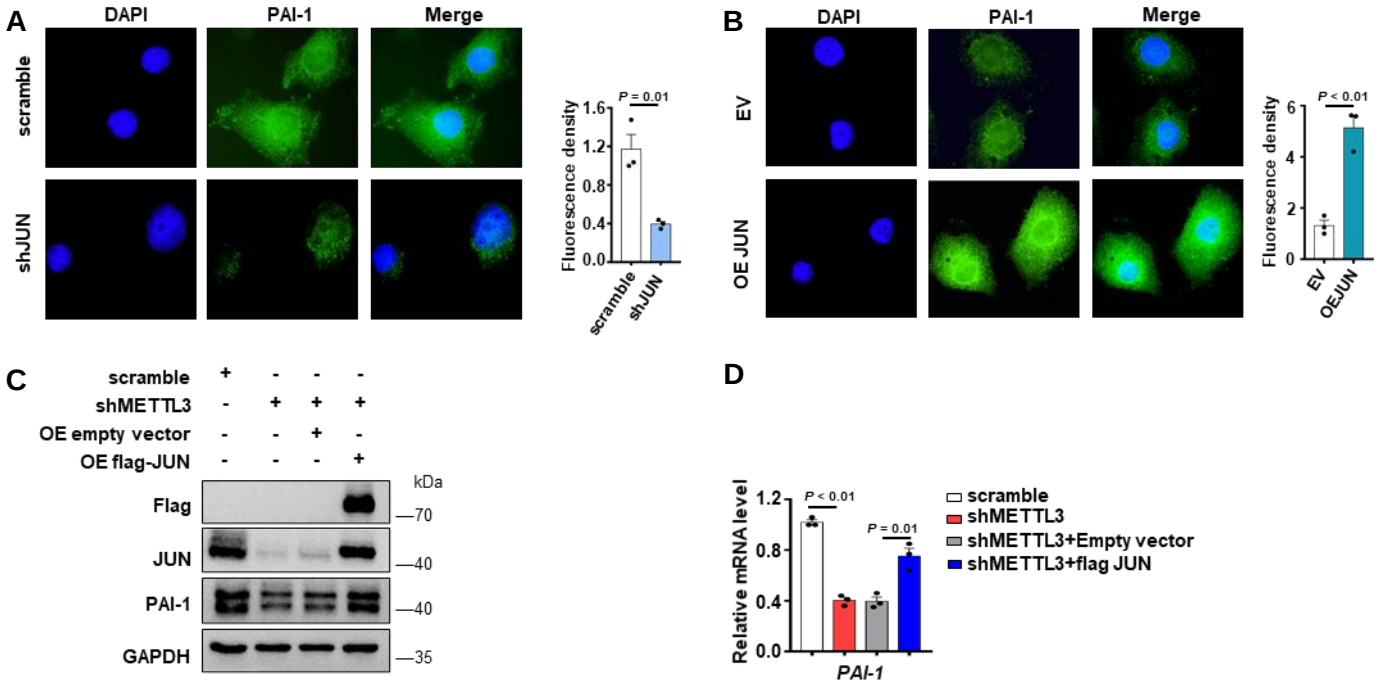


Figure Ⅲ. JUN rescues PAI-1 expression in METTL3 knockdown HUVECs.
(A-B) Immunofluorescence measured the protein of PAI-1 in shJUN and OE JUN HUVECs respectively (n=3, data are mean ± SEM). (C-D) Western blot and qPCR were conducted to detect the protein (A) and mRNA (B) level of PAI-1 in HUVECs after METTL3 or JUN intervention (n=3, data are mean ± SEM), OE: overexpression.

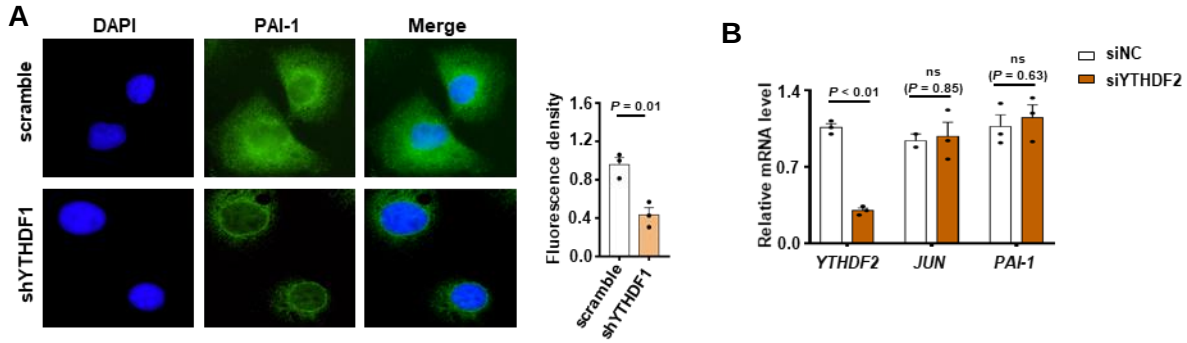


Figure Ⅳ. YTHDF2 has little effect on the expression of *JUN* and *PAI-1* mRNA abundance.
(A). Immunofluorescence measured the protein of PAI-1 in shYTHDF1 HUVECs (n=3, data are mean ± SEM). (B) PCR detected the mRNA level of *JUN* and *PAI-1* in HUVECs afterYTHDF2 knockdown (n=3, data are mean ± SEM).

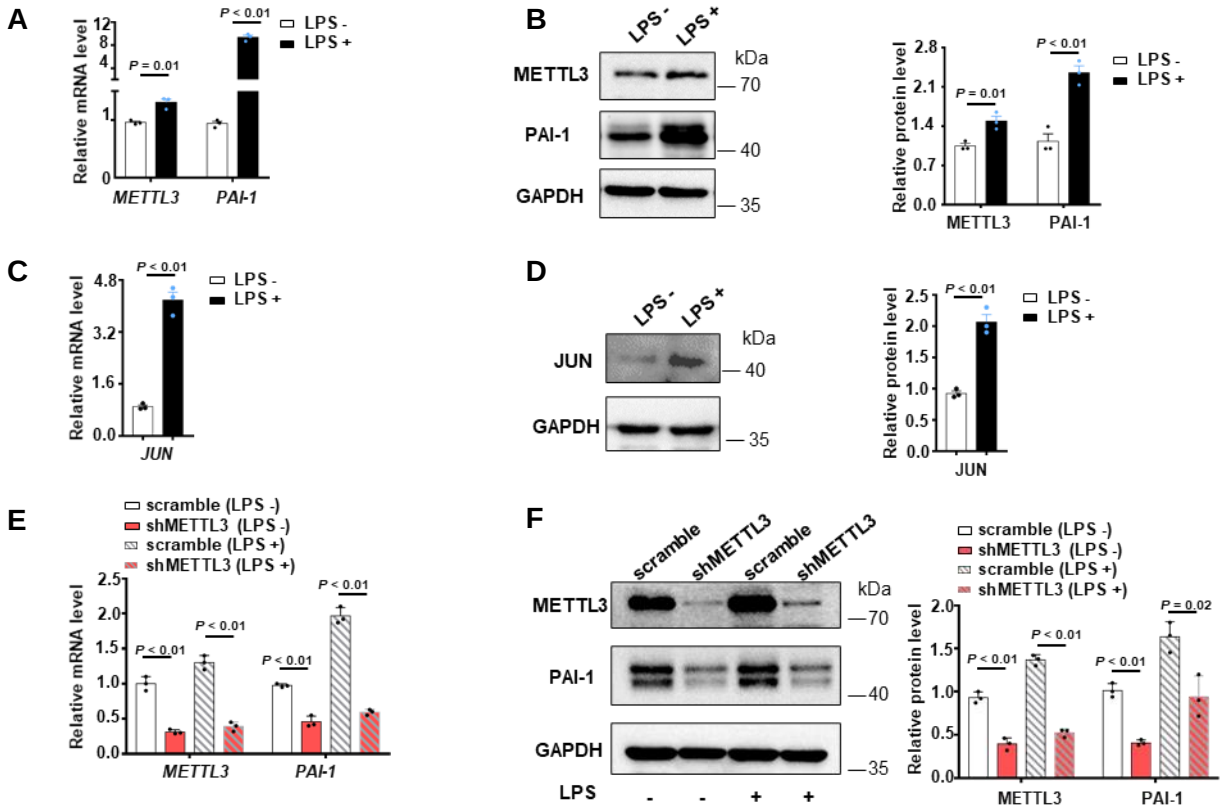
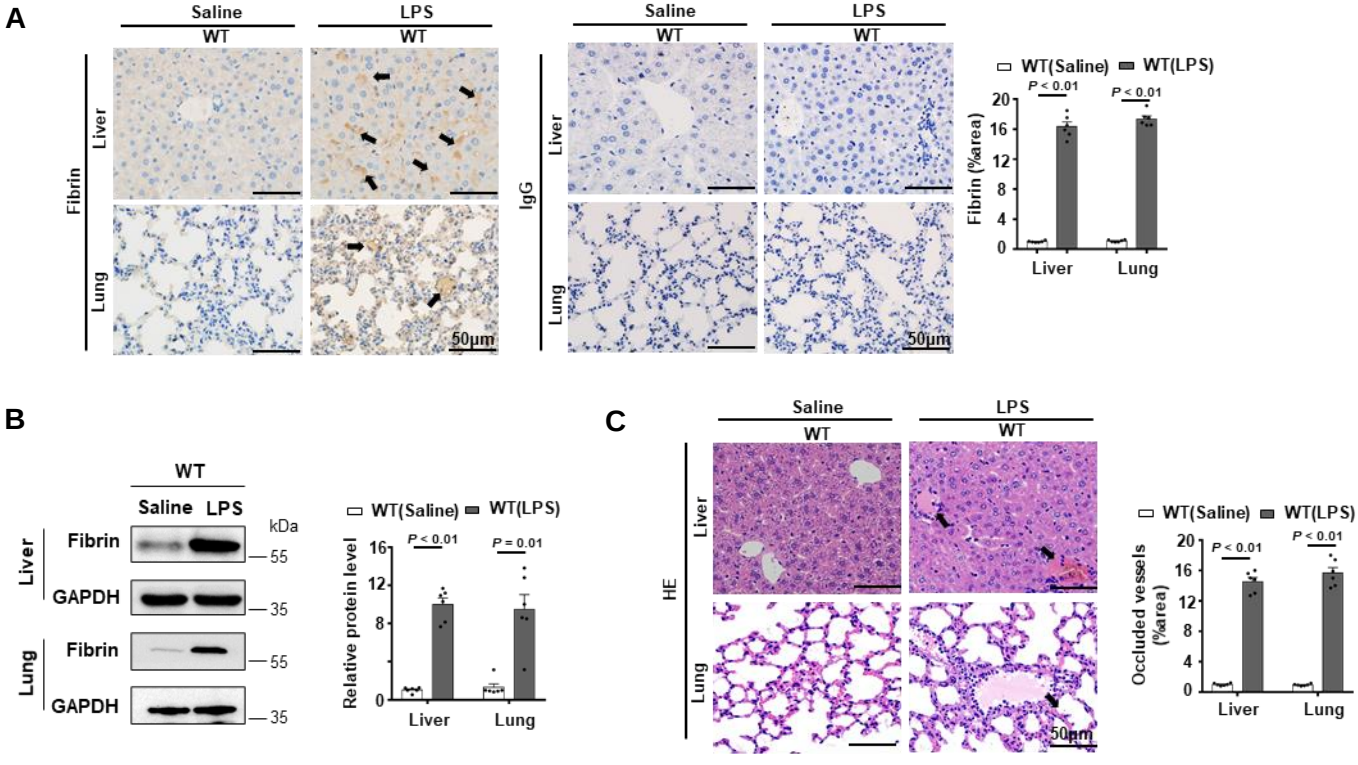


Figure Ⅴ. METTL3/JUN/PAI-1 axis are up-regulated in LPS-treated HUVECs.

(A, B) qPCR (A) and western blot (B) showed the increased METTL3 and PAI-1 expression upon LPS stimulation in HUVECs (n=3, data are mean ± SEM). (C, D) qPCR (C) and western blot (D) analysis of JUN in LPS-treated HUVECs (n=3, data are mean ± SEM). (E, F) qPCR (E) and western blot (F) measured the expression of METTL3 and PAI-1 in LPS challenged shMETTL3 HUVECs (n=3, data are mean ± SEM).



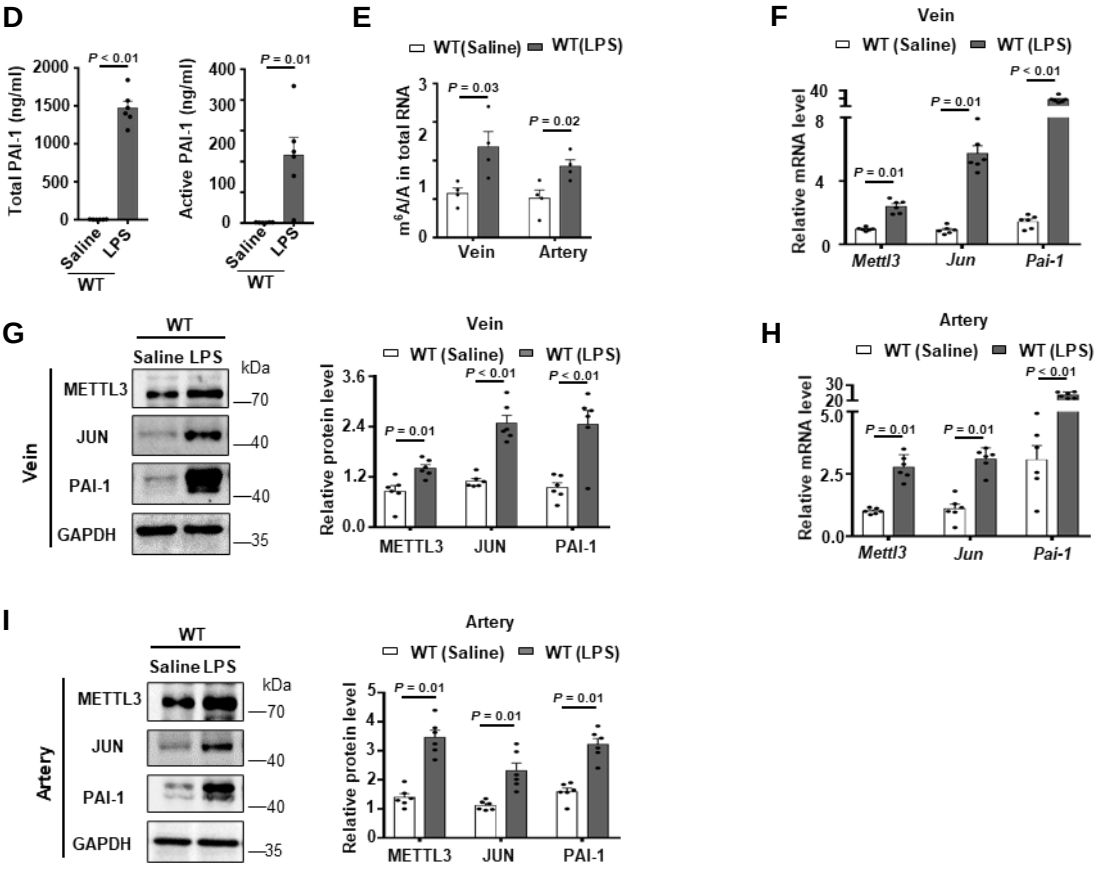
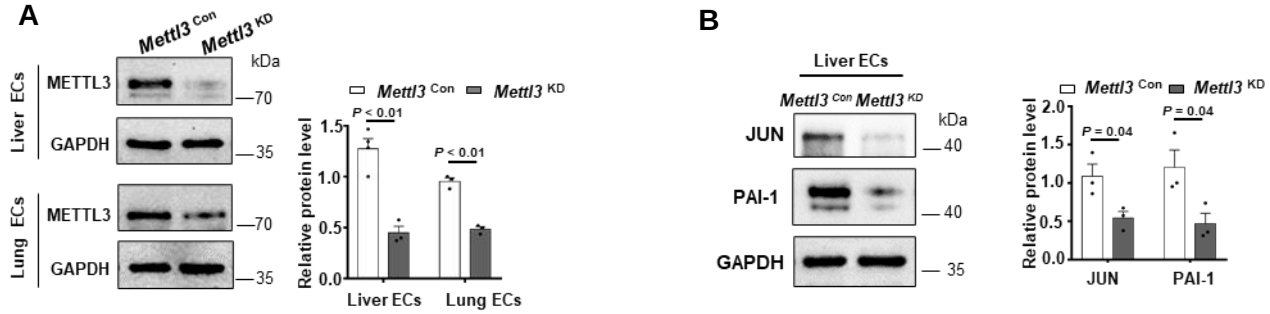


Figure Ⅵ. METTL3/m^{6}A/JUN/PAI-1 axis are up-regulated in endotoxin-treated WT mice.
(A-B) Immunohistochemistry (A) and western blot (B) were used to detect fibrin in livers and lungs of LPS-treated mice (n=6, 3 males and 3 females) and saline-treated mice (n=6, 3 males and 3 females). Data are mean ± SEM, the black arrow indicates fibrin. (C) HE staining was used to detect thrombus in livers and lungs of LPS-treated mice (n=6, 3 males and 3 females) and saline-treated mice (n=6, 3 males and 3 females). Data are mean ± SEM, the black arrow indicates thrombus. (D) The levels of total PAI-1 and active PAI-1 in plasma of LPS challenged mice (n=6, 3 males and 3 females) and saline challenged mice (n=6, 3 males and 3 females) were detected by ELISA, data are mean ± SEM. (E) Overall m^{6}A levels were qualitative using an antibody-mediated m^{6}A capture assay in the vein and artery of LPS-treated mice (n=4, 3 males and 1 females) and saline-treated mice (n=4, 3 males and 1 females), data are mean ± SEM. (F-G) qPCR (F) and western blot (G) analysis of METTL3, JUN and PAI-1 in the vein of saline- treated mice (n=6, 3 males and 3 females) and LPS-treated mice (n=6, 3 males and 3 females), data are mean ± SEM. (H-I) qPCR (H) and western blot (I) analysis of METTL3, JUN and PAI-1 in the artery of saline- treated mice (n=6, 3 males and 3 females) and LPS-treated mice (n=6, 3 males and 3 females), data are median ± SD.



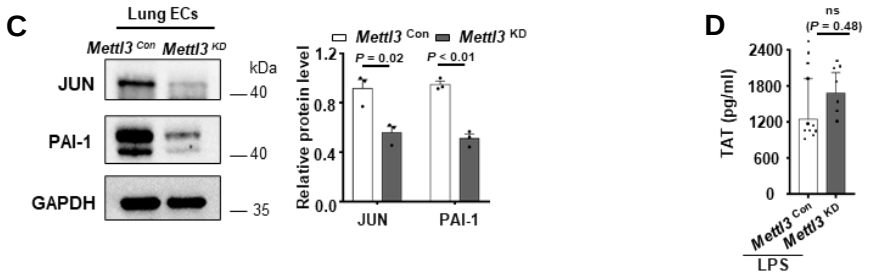


Figure Ⅶ. The protein expression of JUN and PAI-1 are down-regulated in the vascular endothelial cells of *Mettl3* ^{KD} mice.

(A) Western blot analysis of METTL3 in livers and lungs vascular endothelial cells of *Mettl3* ^{Con} mice (n=3, 2 males and 1 females) and *Mettl3* ^{KD} mice (n=3, 2 males and 1 females), data are mean ± SEM. (B-C) Western blot showed the protein expression of JUN/PAI-1 in livers (B) and lungs (C) vascular endothelial cells of *Mettl3* ^{Con} mice (n=3, 2 males and 1 females) and *Mettl3* ^{KD} mice (n=3, 2 males and 1 females), data are mean ± SEM. (D) ELISA showed the levels TAT in plasma of LPS-treated *Mettl3* ^{Con} mice (n=11, 6 males and 5 females) and *Mettl3* ^{KD} mice (n=7, 4 males and 3 females), data are median ± SD.

Table Ⅰ. Differentially Expressed Genes in shMETTL3 HUVECs.

Genes differentially expressed in shMETTL3 HUVECs are listed as follows with adjusted *P*-value < 0.05 and fold change > 2.

Down-regulated genes in shMETTL3 HUVECs:

Gene name	shMETTL3 (read count)	scramble (read count)	log_2FoldChange	*p*-value	padj
SERPINE1 (PAI-1)	2134.936347	5802.243931	-1.442396683	5.41E-104	3.78E-100
HMOX1	1535.131598	4266.740026	-1.474732995	2.63E-98	1.22E-94
OSMR	3521.340596	9290.378909	-1.399638383	7.96E-96	2.78E-92
LAMC2	3226.799314	8074.003894	-1.323185018	2.23E-95	6.23E-92
EMP1	748.7684028	2370.631854	-1.662693698	2.42E-85	4.83E-82
SERPINE2	943.1093203	2753.411255	-1.545680421	5.44E-83	9.51E-80
DEGS1	677.6902426	2009.673539	-1.56836139	5.44E-72	6.90E-69
CALD1	1301.875567	3816.927516	-1.551764152	1.54E-71	1.79E-68
PPP1R3B	549.0898086	1556.997663	-1.503745453	1.84E-61	1.71E-58
PERP	996.1074932	2563.386185	-1.36360799	3.67E-61	3.20E-58
UPP1	2520.355879	6318.642257	-1.325966534	8.44E-59	6.93E-56
POFUT1	1493.022531	3225.010954	-1.111056525	1.69E-55	1.18E-52
IFI6	730.3399096	2273.844143	-1.638510373	3.20E-55	2.13E-52
TPM4	9876.498498	19885.43355	-1.009631425	1.51E-51	9.58E-49
ITGA6	2201.164647	4754.502909	-1.11102047	3.07E-51	1.86E-48
SLC7A11	379.3150902	1080.615506	-1.510383303	7.07E-48	3.66E-45
OAS2	110.4986958	556.2057697	-2.331600676	1.26E-47	6.05E-45
LHFPL2	1093.824939	2351.841137	-1.104389545	1.60E-47	7.45E-45
NPTX1	937.5610834	2257.787793	-1.268008643	6.74E-46	2.94E-43
PSG4	320.4119154	1150.313537	-1.84383927	1.89E-45	7.99E-43
LAMC1	3616.437565	7429.36971	-1.038672784	8.06E-44	3.22E-41
TFPI	543.0266906	1291.201795	-1.249649262	1.33E-43	5.15E-41
EPHB2	172.5804751	582.3497621	-1.754695363	8.63E-43	3.17E-40
CBFB	1330.144271	2777.984549	-1.062422116	2.72E-42	9.74E-40
MME	940.2817606	2033.455151	-1.112712424	1.67E-41	5.82E-39
SYPL1	1185.383211	2546.163884	-1.102940521	4.02E-41	1.34E-38
ASPH	1270.170681	2656.165523	-1.06432509	5.20E-41	1.69E-38
MSANTD3	741.0212424	1675.888219	-1.177304592	3.47E-40	1.10E-37

SLFN5	596.631052	1401.751582	-1.232295417	3.93E-40	1.22E-37
ITGA2	1186.980023	2897.470013	-1.287441633	5.35E-40	1.62E-37
MAP1B	917.2474988	1947.832848	-1.086500127	7.70E-40	2.29E-37
UGT8	268.8376445	743.579587	-1.467658527	3.53E-39	1.03E-36
CXCL6	157.3360181	503.510383	-1.678087114	2.53E-36	6.09E-34
B4GALT6	165.8879426	524.6919741	-1.66100258	6.07E-36	1.44E-33
SLC37A2	95.05161792	376.0382658	-1.984294202	6.35E-36	1.48E-33
NIPAL4	105.9902982	446.2756263	-2.074334168	1.92E-35	4.32E-33
TES	586.6014163	1367.120081	-1.220590193	1.40E-34	2.96E-32
RAB29	718.5749872	1482.622582	-1.045008896	3.71E-34	7.51E-32
MX2	17.46441309	186.7961912	-3.417603812	4.19E-34	8.36E-32
LYN	444.7526603	1008.67756	-1.181373847	1.14E-33	2.20E-31
SNX10	241.0245572	674.2870451	-1.483985416	1.73E-33	3.26E-31
CFL2	456.1202564	1097.024992	-1.266165892	5.56E-31	9.36E-29
SPHK1	724.81477	1531.625794	-1.079318053	6.83E-31	1.12E-28
PKN2	1163.349133	2486.596073	-1.095844281	1.30E-30	2.07E-28
IFI16	151.0071967	471.3317361	-1.64191704	1.80E-30	2.83E-28
STC2	687.919072	1635.067569	-1.249143015	3.55E-30	5.51E-28
4-Mar	291.4073631	741.2622127	-1.346976343	8.36E-30	1.27E-27
C1S	82.21396951	330.6966527	-2.008736217	3.88E-29	5.71E-27
BNIP2	759.3085305	1543.46119	-1.023412723	2.65E-28	3.73E-26
METTL3	514.8106776	1073.922181	-1.060683035	4.66E-27	6.32E-25
TMEM19	301.7594409	702.7871063	-1.219547217	7.28E-27	9.78E-25
NRP1	92.10234514	316.9417389	-1.783305569	5.26E-26	6.87E-24
TXNDC5	204.28686	534.3158079	-1.387231356	3.77E-25	4.58E-23
CTSL	679.9083094	1406.352549	-1.048473765	1.26E-24	1.43E-22
PLPP3	405.7026589	816.9771151	-1.009836274	1.51E-23	1.62E-21
OAS1	110.4940449	327.0760166	-1.565688804	1.56E-23	1.66E-21
FSTL3	391.7904975	870.7809489	-1.152403428	4.01E-23	4.09E-21
CYBRD1	182.3868291	447.0643894	-1.293223562	3.30E-22	3.14E-20
PXDC1	367.0714305	754.2766848	-1.038862518	9.32E-22	8.46E-20
GRB10	415.170307	855.1334106	-1.04249791	2.63E-21	2.31E-19
GLIPR1	24.38466065	145.4522429	-2.575883603	4.08E-21	3.52E-19
GBP3	229.2218116	511.1018014	-1.15678928	5.55E-21	4.70E-19
AL590004.3	12.19717647	111.1989645	-3.188060601	5.77E-21	4.86E-19
ACP7	146.1364243	361.5202665	-1.306768935	2.10E-20	1.71E-18
LGALS3BP	119.5117548	334.3153701	-1.484415035	3.10E-20	2.46E-18
RRAGD	255.6345295	551.7140017	-1.109677743	2.40E-19	1.77E-17
PMP22	321.9798628	651.0563809	-1.015850008	3.90E-19	2.84E-17
ANK2	167.5661865	410.6795902	-1.293144581	3.95E-18	2.64E-16
AL365181.3	135.9812867	331.697368	-1.286610303	3.13E-17	1.93E-15
IFI44	246.6965851	525.0577057	-1.089837364	4.48E-17	2.70E-15
EDEM3	399.2925129	807.8098256	-1.016467872	1.31E-16	7.40E-15
IFI44L	12.86611215	88.55149286	-2.783269944	6.59E-16	3.51E-14
MANEA	308.5641068	639.6895928	-1.051696292	3.02E-15	1.53E-13
GPR137B	126.9688409	288.9934771	-1.186293318	3.02E-14	1.35E-12
PDCD1LG2	5.285339902	63.9185983	-3.597899371	4.06E-14	1.78E-12
ADGRF4	80.81961612	210.5001269	-1.381174445	5.01E-14	2.17E-12
MEGF6	50.84124408	162.4161951	-1.675869428	6.39E-14	2.71E-12
TM4SF19-AS1	117.7931826	263.8889013	-1.163822552	2.60E-13	1.03E-11

SLC35G1	224.565163	452.2870528	-1.009879458	2.77E-13	1.09E-11
GJB3	141.2764578	310.809566	-1.137904647	3.00E-13	1.18E-11
IFI27	14.54577624	86.63112072	-2.576058265	3.15E-13	1.23E-11
TRIM22	10.23729806	70.60210218	-2.787049419	4.06E-13	1.56E-11
AMPD3	45.17506452	141.6434273	-1.648304436	5.24E-13	1.98E-11
GREB1	14.19287103	79.31603346	-2.482884647	6.79E-13	2.55E-11
DNER	88.76170456	219.4257398	-1.305631221	7.68E-13	2.87E-11
KATNBL1	175.1045972	355.067888	-1.019815155	7.78E-13	2.90E-11
LONRF1	81.1919059	206.3490006	-1.345839648	1.40E-12	5.03E-11
ROBO4	32.01620541	121.8272319	-1.927875156	3.54E-12	1.23E-10
HBEGF	103.8807486	233.5716198	-1.168769332	4.01E-12	1.38E-10
LURAP1L	31.33855218	109.3680045	-1.802940963	7.47E-12	2.50E-10
GBP1	27.71162616	99.29226743	-1.841247194	1.82E-11	5.74E-10
SEL1L3	140.2670107	298.254023	-1.088882642	2.36E-11	7.36E-10
PTPRO	24.71729038	100.4768415	-2.02300527	2.62E-11	8.11E-10
AC003092.1	46.18331418	129.6565449	-1.489145955	7.21E-11	2.11E-09
LAMA1	68.95011188	166.925628	-1.275653504	2.05E-10	5.71E-09
GSDMA	28.05439363	95.03241362	-1.760328969	3.16E-10	8.58E-09
SH3TC2	58.07924885	153.4462415	-1.402172389	3.21E-10	8.69E-09
PLSCR4	57.70810149	146.9694404	-1.348383464	4.83E-10	1.27E-08
GBP2	20.45206462	80.57594802	-1.97831594	7.79E-10	2.01E-08
TMEM154	72.58425143	166.2506328	-1.195770617	8.75E-10	2.23E-08
GAL	75.93029496	180.7971744	-1.251717634	1.65E-09	3.97E-08
SPOCD1	1.649250887	39.72492665	-4.589521326	1.79E-09	4.30E-08
STEAP1	82.7981271	183.5510492	-1.148584681	2.58E-09	6.04E-08
CLGN	50.08571973	131.9089379	-1.39649723	5.77E-09	1.29E-07
FGF5	57.08573283	148.7049523	-1.381233502	8.49E-09	1.87E-07
BATF2	10.55881533	54.40468555	-2.364985456	2.08E-08	4.35E-07
AL391422.4	28.71372086	87.08182693	-1.600532681	4.69E-08	9.27E-07
AL356234.3	5.271219394	39.26466164	-2.896185384	5.62E-08	1.09E-06
PCSK1N	65.70171445	161.4620155	-1.297309929	5.68E-08	1.10E-06
BST2	6.929856007	49.54716275	-2.838575937	9.36E-08	1.75E-06
LRP3	54.82280204	137.8996624	-1.330825064	3.10E-07	5.22E-06
TRPM8	28.33730942	82.29964465	-1.537453684	4.18E-07	6.88E-06
TP53I11	58.73879881	127.0783036	-1.113192673	9.51E-07	1.45E-05
PTX3	60.65361422	131.3746659	-1.114385337	1.01E-06	1.52E-05
SUN3	9.886871609	42.61315101	-2.107217525	1.72E-06	2.48E-05
FAM78B	33.66147352	84.2291766	-1.323800069	2.03E-06	2.87E-05
CACNA2D1	58.10523384	124.2582457	-1.097135435	2.18E-06	3.09E-05
SAMD9	29.98182553	81.76105756	-1.446104214	2.48E-06	3.44E-05
ADRB2	44.25641157	104.9230868	-1.246155802	2.55E-06	3.52E-05
ALPK1	57.68699017	122.930293	-1.091175306	2.56E-06	3.54E-05
HTR1D	34.64351548	85.0881729	-1.296000162	4.60E-06	5.95E-05
IL15RA	23.75875466	64.29336721	-1.436521695	6.06E-06	7.61E-05
ACHE	45.85887272	98.98719628	-1.110026172	6.35E-06	7.95E-05
PLIN5	28.70327656	72.01083694	-1.326894371	9.78E-06	0.00011624
ITGB1-DT	50.78206057	109.2142054	-1.104789744	1.79E-05	0.00020167
AC006333.2	31.34125365	76.02217444	-1.278182873	1.90E-05	0.00021223
SATB1	8.58481641	36.00200031	-2.068795133	2.10E-05	0.00023277
IL1B	43.54661839	93.05688141	-1.095232663	2.56E-05	0.00027622

P4HA3	34.65139718	78.23673121	-1.175510429	3.02E-05	0.00031819
AL365203.2	26.09624197	68.41900796	-1.390869749	3.82E-05	0.00039206
AL365181.2	27.04636669	65.57525258	-1.278002145	4.17E-05	0.00042281
PLXNB3	36.9557698	79.34530666	-1.102302252	5.19E-05	0.0005139
FA2H	16.51136416	47.33326983	-1.519985749	7.62E-05	0.00072002
RAG1	27.03945972	64.05367879	-1.243514075	7.68E-05	0.00072482
MMP1	8.583089667	33.01015802	-1.943667488	7.68E-05	0.00072482
IGSF10	41.57757698	86.52232609	-1.057914717	8.49E-05	0.00079045
SAMD9L	42.52867644	87.55303974	-1.041701156	0.00010037	0.00091148
CEACAM19	29.36605728	68.03468024	-1.211955254	0.00010125	0.00091829
AC008429.1	8.891461158	33.30640128	-1.904153608	0.0001016	0.00091969
RGPD6	12.52236994	54.17275979	-2.112937953	0.00010439	0.00094184
TNFSF14	30.33105452	68.36318404	-1.1717643	0.00011856	0.00105205
FEZF1-AS1	12.87970337	39.68018704	-1.623855635	0.00016134	0.00137658
NCF2	21.77687404	53.01267784	-1.283459825	0.00020764	0.00172114
PRKCQ	35.96283811	75.44017544	-1.068295645	0.00024999	0.00201826
PRPS1P2	28.36006365	64.70557334	-1.189507179	0.00025657	0.00206374
S100A3	43.54503053	88.36862413	-1.020794294	0.00027257	0.00217659
MSRB2	29.01810958	62.3128561	-1.102315314	0.00035875	0.00273953
AC005077.4	16.18639341	42.33370187	-1.387809407	0.00045376	0.00333106
CEACAM1	27.6992324	60.96884021	-1.138047114	0.00048353	0.00351831
SERTAD4-AS1	37.57552083	76.00106527	-1.01563427	0.0004843	0.00352123
AC008894.3	18.1489733	44.60713696	-1.297962934	0.00049726	0.00358728
RP1	17.82572929	44.69522142	-1.326244338	0.00050047	0.00360128
PDE2A	16.82123968	42.98891569	-1.353536994	0.0006437	0.0044552
VSIR	32.3591956	70.73545597	-1.128356595	0.00070756	0.0048254
AC026461.3	13.86227461	38.39046957	-1.469320385	0.00084796	0.00565858
GOLGA7B	9.87793133	31.98375941	-1.693882299	0.00090079	0.00594021
AXIN2	17.15927236	41.34640012	-1.268723574	0.00091429	0.00601221
HNF4G	31.66396837	63.59082542	-1.006206125	0.00097986	0.00637134
MTX1P1	56.1322935	174.6042011	-1.637221774	0.00103211	0.00666459
CDKN1C	17.81041132	41.65412668	-1.225594414	0.00119572	0.00758431
TMEM158	122.2307787	313.8089166	-1.360337703	0.0012337	0.00779334
KLF9	11.52943825	32.71623825	-1.50311033	0.00136364	0.00847615
AC002401.4	16.8469181	41.37859359	-1.29674998	0.00148939	0.0091439
CXCR6	12.52732745	33.29982981	-1.410226138	0.00175055	0.01046936
PSG1	17.16370058	41.28267704	-1.26681967	0.00185829	0.01095139
SHISA3	19.12260426	42.93634398	-1.166992491	0.00198087	0.01155189
TBILA	23.06901423	48.66805884	-1.076260613	0.00211812	0.01221963
AL590666.2	27.05252166	56.7593017	-1.068496997	0.00220455	0.01266599
AC017100.1	12.18110649	34.63827002	-1.506674104	0.00224157	0.01284168
AC005865.2	10.87506852	29.97603374	-1.462263847	0.00261944	0.01468715
NIPAL2	17.13674086	39.00426304	-1.185720026	0.00278162	0.01547225
BCAN	25.73935399	52.31079991	-1.023357093	0.0028576	0.01585071
GLIDR	22.06324332	47.92934047	-1.118639442	0.00302337	0.01659232
BTBD19	16.51999788	37.9729526	-1.201857354	0.00356669	0.01896308
ACSM4	14.17680106	31.98017529	-1.173369638	0.00615231	0.02962749
VEPH1	16.48387516	35.6547779	-1.112635029	0.00625116	0.02998283
CYYR1	20.78889985	41.64297531	-1.002537462	0.00646302	0.0307367
TMED6	11.21265576	26.98160311	-1.266771509	0.00729656	0.03397036

TMEM151B	11.90584968	29.69751332	-1.319728733	0.00783122	0.03589716
GPR17	15.16920347	32.97205694	-1.120063873	0.00883295	0.03964325
ENPEP	14.20256332	31.99199051	-1.17228171	0.00885	0.03968154
FAM71F2	15.52737275	35.01071544	-1.173595011	0.00933873	0.04146027
MSR1	18.80454048	38.01437295	-1.015229743	0.01058561	0.04601592

UP regulated genes in shMETTL3 HUVECs:

Gene Name	**shMETTL3 (read count)**	**scramble (read count)**	**log_2FoldChange**	***p*-value**	**padj**
TNC	842.7203087	82.9456316	3.344545612	4.40E-126	6.15E-122
SAA1	759.6426617	92.8721495	3.031224454	1.10E-92	2.56E-89
PEG10	4216.268574	1551.46535	1.44240732	1.56E-80	2.42E-77
ABCA12	441.3329223	36.3478279	3.602668163	1.49E-77	2.08E-74
SRGAP3	421.6145475	48.6493402	3.115382402	3.58E-69	3.84E-66
CBX5	2912.860079	1070.48986	1.444192574	1.64E-65	1.64E-62
NPNT	1198.493163	401.816239	1.576600455	7.67E-57	5.95E-54
SLC48A1	5093.120756	2099.8067	1.278331765	9.35E-57	6.88E-54
TNFAIP2	13403.89179	5931.48513	1.176217746	2.04E-50	1.18E-47
ADORA1	856.6729531	271.275611	1.658966544	1.02E-49	5.69E-47
KLHDC3	1771.2536	771.362962	1.19925186	2.36E-49	1.27E-46
C1orf216	1350.144385	537.629251	1.328494809	1.08E-47	5.38E-45
RAPGEF3	1481.56854	592.633198	1.322185702	7.76E-43	2.93E-40
ELF3	925.7554738	359.497272	1.364557725	6.69E-39	1.91E-36
COL12A1	1804.803731	788.330292	1.194847731	6.08E-38	1.63E-35
CCDC198	666.1882985	219.104003	1.604005742	4.69E-37	1.24E-34
CBX1	2952.550479	1439.59941	1.036230607	5.85E-37	1.51E-34
VCAN	1303.168344	550.133142	1.243972998	1.79E-36	4.38E-34
PTAFR	627.5612704	226.316739	1.471498059	4.90E-35	1.09E-32
KLHL14	196.311518	28.3423461	2.792654123	1.93E-32	3.50E-30
NEURL1B	688.0297538	258.319813	1.413368891	2.15E-32	3.86E-30
ALPK2	416.9434168	131.96682	1.659740013	5.63E-31	9.36E-29
BX571818.1	1074.636076	438.757875	1.292035769	7.22E-31	1.17E-28
MPP3	832.2695601	316.020018	1.397256885	4.53E-30	6.96E-28
MYLK	303.5754077	82.9393921	1.871564064	2.41E-28	3.43E-26
WNT10A	164.3433837	29.3421269	2.486082556	7.83E-24	8.61E-22
IKBKE	860.8534558	426.164705	1.014274957	3.71E-23	3.81E-21
RNF152	224.0962255	54.6857943	2.035222975	5.29E-23	5.31E-21
CGN	795.2040179	372.666539	1.09315939	6.80E-23	6.74E-21
FAT4	802.7852145	390.707598	1.038792028	1.13E-22	1.11E-20
ARL1	995.9464581	454.029591	1.132996895	1.19E-22	1.16E-20
SH3D21	434.2461765	176.23105	1.300825727	7.41E-22	6.80E-20
SERPINA6	154.811144	25.3610583	2.610795678	2.78E-21	2.43E-19
B3GALT5	395.8773945	155.354603	1.349724813	1.42E-20	1.16E-18
DENND2A	519.4456254	227.355881	1.192118636	2.91E-20	2.32E-18
CDH1	153.4289616	32.0330789	2.260952003	5.13E-20	4.00E-18
MAP3K12	918.0995819	425.265292	1.110507688	8.16E-20	6.26E-18
NRG1	686.749512	325.363477	1.077919647	1.63E-19	1.23E-17
H19	244.383157	46.0608762	2.408230075	1.68E-19	1.26E-17
SAA2	104.5445879	11.9828992	3.124067447	2.13E-19	1.59E-17
KCNJ16	95.72086016	8.97207346	3.412344019	1.07E-18	7.52E-17
CSGALNACT1	218.0229698	70.0185106	1.639114632	2.15E-18	1.47E-16

PAX2	341.9426594	132.018396	1.373117978	1.21E-17	7.85E-16
WNT6	137.0581056	21.9921907	2.639461342	2.33E-17	1.45E-15
ARMH4	556.5436928	265.562018	1.067403444	4.34E-17	2.63E-15
ADAP1	328.0341794	122.018861	1.4268865	4.48E-17	2.70E-15
SH3PXD2A	311.1728342	126.651959	1.29687466	6.56E-17	3.83E-15
GRB14	289.2401341	113.065641	1.355693671	1.60E-16	8.92E-15
SYT8	110.8824046	22.3045643	2.312693069	7.20E-16	3.82E-14
MT1F	766.3121674	359.43985	1.091894778	7.97E-16	4.20E-14
TNFRSF19	357.1909366	161.967745	1.141119716	1.11E-15	5.78E-14
THEG	163.615571	49.606373	1.721111338	6.16E-15	3.01E-13
SYT11	229.9707355	88.7066197	1.374759269	7.34E-15	3.55E-13
TRIB2	293.3186412	124.238199	1.239060012	9.29E-15	4.40E-13
POU5F1	389.4959561	166.979263	1.221894064	3.88E-14	1.71E-12
CXCL3	331.1293972	151.834857	1.124561422	9.45E-14	3.95E-12
ITGB2	136.2876249	40.266434	1.75795529	3.04E-13	1.19E-11
DHRS2	335.4443081	153.849885	1.124269462	4.11E-13	1.58E-11
SLCO2B1	269.4858305	116.999314	1.203916132	4.28E-13	1.64E-11
CBLN2	156.3636685	53.61074	1.543832563	1.16E-12	4.19E-11
PRRT3	286.2044902	124.988401	1.195182566	1.64E-12	5.86E-11
FER1L4	83.82408964	17.0235556	2.30112929	2.44E-12	8.57E-11
SLC22A3	159.5967479	53.3332154	1.581643825	3.22E-12	1.13E-10
VCAM1	52.10049231	4.00669053	3.703115917	8.32E-12	2.75E-10
NOVA2	308.6102783	147.727541	1.063049082	3.11E-11	9.57E-10
DNAJC6	352.9718324	175.616992	1.007141965	6.01E-11	1.78E-09
KIF12	284.5174449	134.350046	1.082583991	7.11E-11	2.09E-09
MAL2	241.7700276	112.551808	1.102707561	7.38E-11	2.15E-09
TMEM243	293.8341457	144.845618	1.020212382	1.63E-10	4.59E-09
PGM5	114.8362509	38.2731119	1.58420263	2.97E-10	8.08E-09
AKAP5	168.5150299	70.3308841	1.260919006	1.20E-09	2.97E-08
PANK1	133.903209	51.3086956	1.383888755	1.25E-09	3.08E-08
LYSMD2	147.4606206	59.3138456	1.313878927	2.35E-09	5.54E-08
PTPN13	86.10022124	24.7065084	1.802524005	2.50E-09	5.87E-08
ISM1	79.41565429	21.3652543	1.895722407	1.30E-08	2.80E-07
CP	39.26351207	3.65754363	3.421976971	1.39E-08	2.98E-07
TMEFF2	57.39176445	13.3393942	2.105843485	1.75E-08	3.69E-07
KCNIP3	114.4315984	40.6848797	1.49248073	1.79E-08	3.78E-07
PLLP	178.1664437	84.9732058	1.068097638	5.25E-08	1.03E-06
RAB19	175.9700776	80.6364189	1.125576703	1.16E-07	2.11E-06
CRISPLD2	62.04557269	16.6671734	1.896439092	1.21E-07	2.20E-06
RAB39B	78.14078153	22.9213451	1.767509971	1.29E-07	2.34E-06
PSORS1C3	119.7797142	50.9677798	1.232440028	1.47E-07	2.62E-06
KLHDC7A	38.26375724	6.32121405	2.596261963	2.32E-07	4.01E-06
SEMA5A	140.1780821	64.3239681	1.123987391	3.20E-07	5.35E-06
RAB17	109.9068793	41.5910004	1.4010486	1.24E-06	1.84E-05
PIANP	125.4279582	60.9675796	1.040421044	3.62E-06	4.80E-05
SOCS1	149.4742245	72.402068	1.046343087	4.18E-06	5.48E-05
FZD10-DT	93.76518725	40.9647278	1.194066424	8.40E-06	0.0001014
SERPINB9	94.09826243	43.0033863	1.12965721	2.05E-05	0.0002282
CNIH2	46.87845757	14.351986	1.708576563	2.28E-05	0.0002503
CRB3	116.1516746	57.9560229	1.00264937	2.74E-05	0.000292

AQP3	49.79146874	16.6885474	1.57833474	2.87E-05	0.0003044
HOXA3	135.341344	64.6355437	1.065978182	3.77E-05	0.0003886
SLC47A2	46.18827169	14.9493844	1.625251712	4.28E-05	0.0004333
DLL1	80.20384787	36.0144794	1.155349088	4.74E-05	0.0004744
RASD2	58.45340426	20.6058258	1.502320184	5.12E-05	0.0005079
C6orf58	40.55949615	11.9776555	1.758730268	6.61E-05	0.0006414
AC091806.1	31.68973064	7.9775364	1.987809478	7.31E-05	0.0006955
SGK2	50.21759412	16.9762276	1.563531548	7.80E-05	0.0007345
SLC4A8	40.25232211	12.6351928	1.669998891	8.26E-05	0.0007724
FRMPD3	51.14549392	18.9754574	1.429726363	8.78E-05	0.0008138
AP001527.2	72.89434966	34.319657	1.086777146	0.0001419	0.0012238
CYS1	81.16703453	38.388478	1.081160214	0.0001501	0.0012867
AC092868.1	30.66616301	8.65578388	1.824340634	0.000208	0.0017229
SAMD14	66.34533331	30.3373278	1.12896865	0.0002248	0.0018448
ZNF608	79.20303447	38.6991919	1.033786931	0.0002577	0.0020695
PRRT2	55.09159732	23.2767315	1.241588281	0.0002734	0.0021809
PTP4A3	71.20919878	34.6359465	1.039692952	0.0003755	0.002844
FAM57B	53.79653294	23.65774	1.184990141	0.0004878	0.003543
AC004890.2	69.92644432	34.6839383	1.012117767	0.0004991	0.0035934
C9orf84	40.54626653	15.6545816	1.372942628	0.0007733	0.0052176
PREX2	40.2557756	16.0089722	1.330820371	0.0008061	0.0054053
KDF1	63.06785902	30.0029834	1.071720203	0.0010696	0.0068686
VGLL3	59.64642313	27.3201954	1.126710211	0.0011246	0.0071757
RHBDL1	39.27320436	16.0083084	1.29511161	0.001538	0.0093807
RHEX	40.95512448	16.9821353	1.269143604	0.0016342	0.0098729
ITGB2-AS1	47.78104054	21.0013049	1.186528441	0.0020041	0.0116628
DNAH3	33.64810503	13.2979738	1.337770136	0.0023956	0.0135516
MIR4664	50.53805282	23.2947863	1.116229216	0.0029565	0.0163149
AL157829.1	34.6170012	14.6541369	1.240048008	0.0031315	0.0170918
HOXA-AS2	28.03952111	10.6553455	1.395372867	0.0033509	0.0180286
ACTL10	45.19157994	20.5989224	1.131822143	0.0036969	0.0195067
4-Sep	29.0225378	11.3398325	1.356483085	0.0036998	0.0195119
AP003392.4	46.21425667	22.981484	1.007306141	0.0042233	0.0218148
NFATC4	41.92184847	20.0156628	1.067022768	0.0043915	0.0225002
BCL11B	28.35780762	10.6944424	1.408921676	0.0046042	0.0233298
CDHR5	37.66578571	15.7032372	1.263193837	0.0051956	0.0257422
TNFAIP6	31.6662244	12.6930083	1.320380779	0.005674	0.0276899
LINC02298	32.97788805	14.9628592	1.13885827	0.0078135	0.0358511
CACNB4	41.8402173	20.2984312	1.043191063	0.0093145	0.0413924
AC011330.1	46.21236225	18.2166927	1.340673695	0.0103476	0.0451639

Table Ⅱ. Comparation of whole blood profile between *Mettl3* ^{Con} and *Mettl3* ^{KD} mice.

Parameter (units)	***Mettl3* ^{Con} mice (n=11,median ± SD)**	***Mettl3* ^{KD} mice (n=7, median ± SD)**	***P value***
White blood cells ($\times10^9$/L)	5.75±3.8	9.3±2.4	0.15
Lymphocytes ($\times10^9$/L)	4.3±2.2	5.9±1.9	0.14
Monocytes ($\times10^9$/L)	0.3±0.1	0.3±0.06	0.91
Granulocyte ($\times10^9$/L)	2.7±1.3	3.3±1.4	0.41
Red blood cells ($\times10^{12}$/L)	10.2±2.1	9.36±1.4	0.64
Platelets ($\times10^9$/L)	1317±275	1291±399.9	0.44