Supplementary Table1. Clinical characteristics of the enrolled subjects

Clinical characteristics	Control (n = 210)	CAD (n = 180)	P value
Age (years)	58.5 (52.50-69.25)	62 (55.00-67.00)	0.4834
Sex, male (%)	129 (61.40%)	117 (65.00%)	0.4660
Diabetes, yes (%)	17 (8.10%)	39 (21.67%)	**<0.0001**
Hypertension, yes (%)	53 (25.24%)	116 (64.44%)	**<0.0001**
FPG (mmol/L)	5.36(5.04-5.77)	5.75(5.14-6.83)	**<0.0001**
TC (mmol/L)	4.51(4.04-4.85)	4.15(3.51-4.92)	**0.0198**
TG (mmol/L)	1.08(0.87-1.33)	1.38(0.98-1.87)	**<0.0001**
LDL-C (mmol/L)	2.66(2.26-3.04)	2.47(1.91-3.16)	0.2029
HDL-C (mmol/L)	1.37(1.21-1.58)	1.12(0.88-1.38)	**<0.0001**
Hcy (μmol/L)	9.20 (2.93-10.95)	11.52 (3.26-11.52)	**<0.0001**
Leukocytes ($\times 10^9$)	5.64(4.80-6.41)	5.95(4.96-7.04)	**0.0383**
Neutrophil ($\times 10^9$)	3.05(2.55-3.60)	3.72(2.98-4.69)	**<0.0001**
Monocyte ($\times 10^9$)	0.39(0.32-0.47)	0.48(0.38-0.63)	**<0.0001**
Lymphocyte ($\times 10^9$)	1.92(1.62-2.32)	1.50(1.16-1.83)	**<0.0001**

Data are presented as median (interquartile range) or n (%).

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine. Significant P values were in bold.

Supplementary Table2. Clinical characteristics of the randomly selected subjects

Clinical characteristics	Control (n = 112)	CAD (n = 110)	P value
Age (years)	60 (53.25-70.00)	61 (55.00-67.00)	0.8515
Sex, male (%)	70 (48.95%)	73 (51.05%)	0.5477
Diabetes, yes (%)	5 (4.46%)	22 (20.00%)	**0.0004**
Hypertension, yes (%)	33 (32.35%)	69 (67.65%)	**<0.0001**
FPG (mmol/L)	5.43(5.13-5.76)	5.75(5.15-6.74)	**0.0008**
TC (mmol/L)	4.49(4.02-4.84)	4.16(3.45-4.94)	0.1588
TG (mmol/L)	1.12(0.86-1.36)	1.49(0.97-1.88)	**<0.0001**
LDL-C (mmol/L)	2.68(2.25-3.04)	2.48(1.89-3.15)	0.4028
HDL-C (mmol/L)	1.41(1.24-1.63)	1.12(0.88-1.37)	**<0.0001**
Hcy (μmol/L)	8.94 (2.93-8.94)	11.52 (3.26-11.52)	**<0.0001**
Leukocytes ($\times 10^9$)	5.69(4.80-6.13)	5.80(4.94-6.75)	0.7891
Neutrophil ($\times 10^9$)	2.99(2.51-3.67)	3.57(2.72-4.33)	**0.0018**
Monocyte ($\times 10^9$)	0.40(0.33-0.48)	0.44(0.37-0.54)	**0.0041**
Lymphocyte ($\times 10^9$)	1.96(1.66-2.33)	1.55(1.23-1.86)	**<0.0001**

Data are presented as median (interquartile range) or n (%).

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine.

Significant P values were in bold.

Supplementary Table 3. Independent risk factors for CAD

Parameters	Multivariate regressions	
	β(95%CI)	P
FPG	1.56(1.11 - 2.21)	**0.011**
LDL-C	0.55(0.32 - 0.94)	**0.028**
TG	3.63(1.53 - 8.63)	**0.004**
HDL-C	0.31(0.10 - 0.92)	**0.035**
Hcy	1.14(1.05 - 1.24)	**0.003**
cg25953130 Methy.	1.03(1.01 - 1.05)	**0.012**

Backfoward multivariate regression analysis was used to analyze the independent risk factors for CAD. Adjust for age, FPG, TC, TG, LDL-C, HDL-C, Hcy and leukocyte count.

Abbreviations: Methy., methylation; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; 95%CI, 95% confidence interval.

Significant P values were in bold.

Supplementary Table 4. Bivariate and multivariate association between clinical parameters and the methylation levels of cg25953130

Groups	Parameters	cg25953130 methylation levels（%）			
		Univariate correlations		Multivariate regressions	
		r	P	β(95%CI)	P
Control	Age	-0.2305	**0.0145**	-0.24(-0.59 - -0.10)	**0.0059**
	FPG	-0.1795	0.0606	-	-
	TC	0.0736	0.4404	-	-
	TG	0.2804	**0.0027**	0.21 (1.06 - 21.25)	**0.0307**
	LDL-C	0.2984	**0.0014**	-	-
	HDL-C	-0.1617	0.0884	-0.03(-13.70 - 9.50)	0.7206
	Hcy	0.2589	**0.0058**	0.27 (0.45 - 2.04)	**0.0024**
	Leukocytes	-0.1062	0.2649	-	-
CAD	Age	0.0986	0.3054	0.14(-0.09 - 0.66)	0.1375
	FPG	-0.0504	0.6080	-	-
	TC	-0.0781	0.4354	-	-
	TG	0.0869	0.3848	-0.01(-2.78 - 2.59)	0.9435
	LDL-C	-0.0775	0.4389	-	-
	HDL-C	-0.2907	**0.0030**	-0.33(-23.82 - -6.33)	**0.0009**
	Hcy	-0.1118	0.2492	-0.08(-0.73 - 0.29)	0.3867
	Leukocytes	-0.1000	0.2986	-	-

In order to control the influence of confounding factors on the linear regression model, in the multivariate regression analysis, we first use Stepwise's statistical method to eliminate the variables with collinearity and establish the optimal regression model, in which the age, TG, Hcy and HDL-C parameters are incorporate into the regression model.

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; 95%CI, 95% confidence interval.

Significant P values were in bold.

Supplementary Table 5. Serum lipids, Hcy and FPG levels of mouse

groups	Contents					
	TC (mmol/L)	TG (mmol/L)	LDL-C(mmol/L)	HDL-C(mmol/L)	FPG (mmol/L)	Hcy(μmol/L)
G1	2.54±0.58	0.65±0.20	0.24±0.08	1.59±0.20	3.14±1.21	15.04±1.75
G2	14.94±2.47	0.75±0.08	2.22±0.44	0.71±0.13	3.24±1.13	13.97±2.10
G3	20.46±7.87	0.97±0.60	4.09±2.46	0.66±0.15	5.21±1.79	9.21±1.14
G4	13.38±2.70	0.65±0.22	1.86±0.42	0.72±0.10	3.98±1.06	12.83±1.27
G5	14.89±2.71	0.95±0.29	2.45(2.19-2.50)	0.82±0.16	2.78±0.53	28.77±7.85
G6	11.16±1.91	0.66±0.13	1.95±0.17	0.55±0.11	2.57±0.73	19.52±3.95
G7	15.98±3.49	0.77±0.15	2.54±0.67	0.75±0.15	3.82±0.84	30.90±8.14

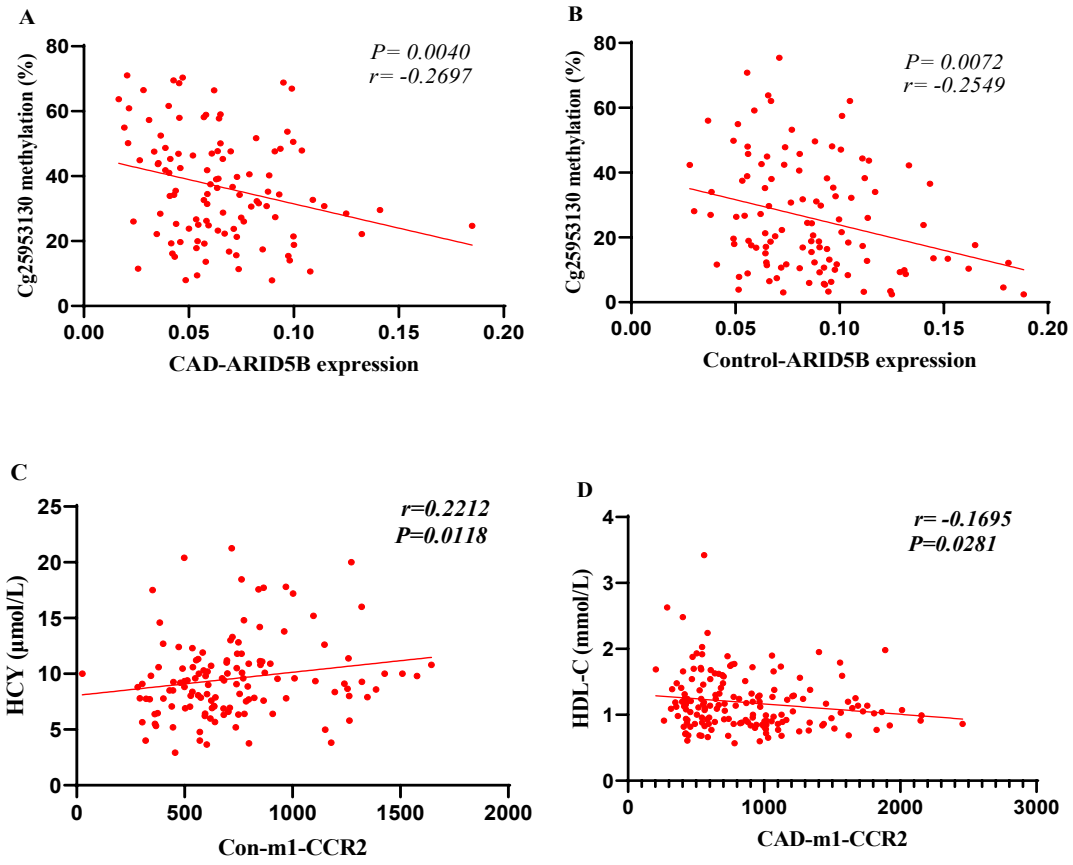
Data are presented as mean ± SD (standard deviation) or as median (interquartile range).

Mice were divided into seven subgroups: G1, ApoE-WT + ND; G2, ApoE-/- + ND; G3, ApoE-/- + HFD; G4, ApoE-/- + HFD + FA; G5, ApoE-/- + ND + Hcy; G6, ApoE-/- + ND + Hcy + FA; G7, ApoE-/- + HFD + Hcy + FA.

Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; WT, wild type; ND, normal diet; HFD, high fat diet; FA, folic acid.

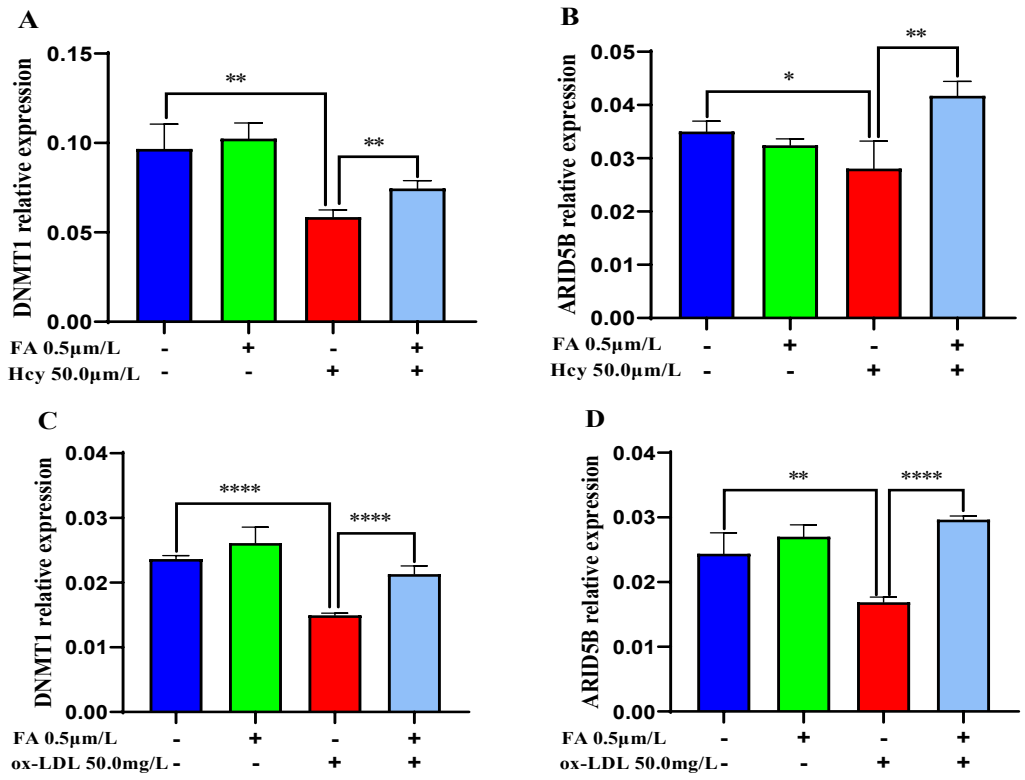
Supplementary Table 6. Primers for RT-qPCR

Species	Gene Name	Primers（5'to3'）
Human	GAPDH	Forward：GAAGGTGAAGGTCGGAGTC
		Reverse：GAAGATGGTGATGGGATTTC
	DNMT1	Forward：ACCGCTTCTACTTCCTCGAGGCCTA
		Reverse：GTTGCAGTCCTCTGTGAACACTGTGG
	ARID5B	Forward：GAATTAGGCGGTAATCCTGGGAG
		Reverse：TCCGAGGTTTGATTGGAGGCAG
	MCP-1	Forward：AAGTGTCCCAAAGAAGCTGTG
		Reverse：AGTTTGGGTTTGCTTGTCCAG
	CCR2	Forward：TACGGTGCTCCCTGTCATAAA
		Reverse：TAAGATGAGGACGACCAGCAT
	CD86	Forward：CTGCTCATCTATACACGGTTACC
		Reverse：GGAAACGTCGTACAGTTCTGTG
	IL-10	Forward：GACTTTAAGGGTTACCTGGGTTG
		Reverse：TCACATGCGCCTTGATGTCTG
	Arg-1	Forward：TGGACAGACTAGGAATTGGCA
		Reverse：CCAGTCCGTCAACATCAAAACT
	TNF-α	Forward：AGAACTCACTGGGGCCTACA
		Reverse：GCTCCGTGTCTCAAGGAAGT
Mouse	GAPDH	Forward：AGGTCGGTGTGAACGGATTTG
		Reverse：TGTAGACCATGTAGTTGAGGTCA
	DNMT1	Forward：AAGAATGGTGTTGTCTACCGAC
		Reverse：CATCCAGGTTGCTCCCCTTG
	ARID5B	Forward：TTCCTCCCCGAAGACACTCC
		Reverse：CTGTCCGTTTCTCCCGAAGG
	MCP-1	Forward：TAAAAACCTGGATCGGAACCAAA
		Reverse：GCATTAGCTTCAGATTTACGGGT
	TNF-α	Forward：CCCTCACACTCAGATCATCTTCT
		Reverse：GCTACGACGTGGGCTACAG



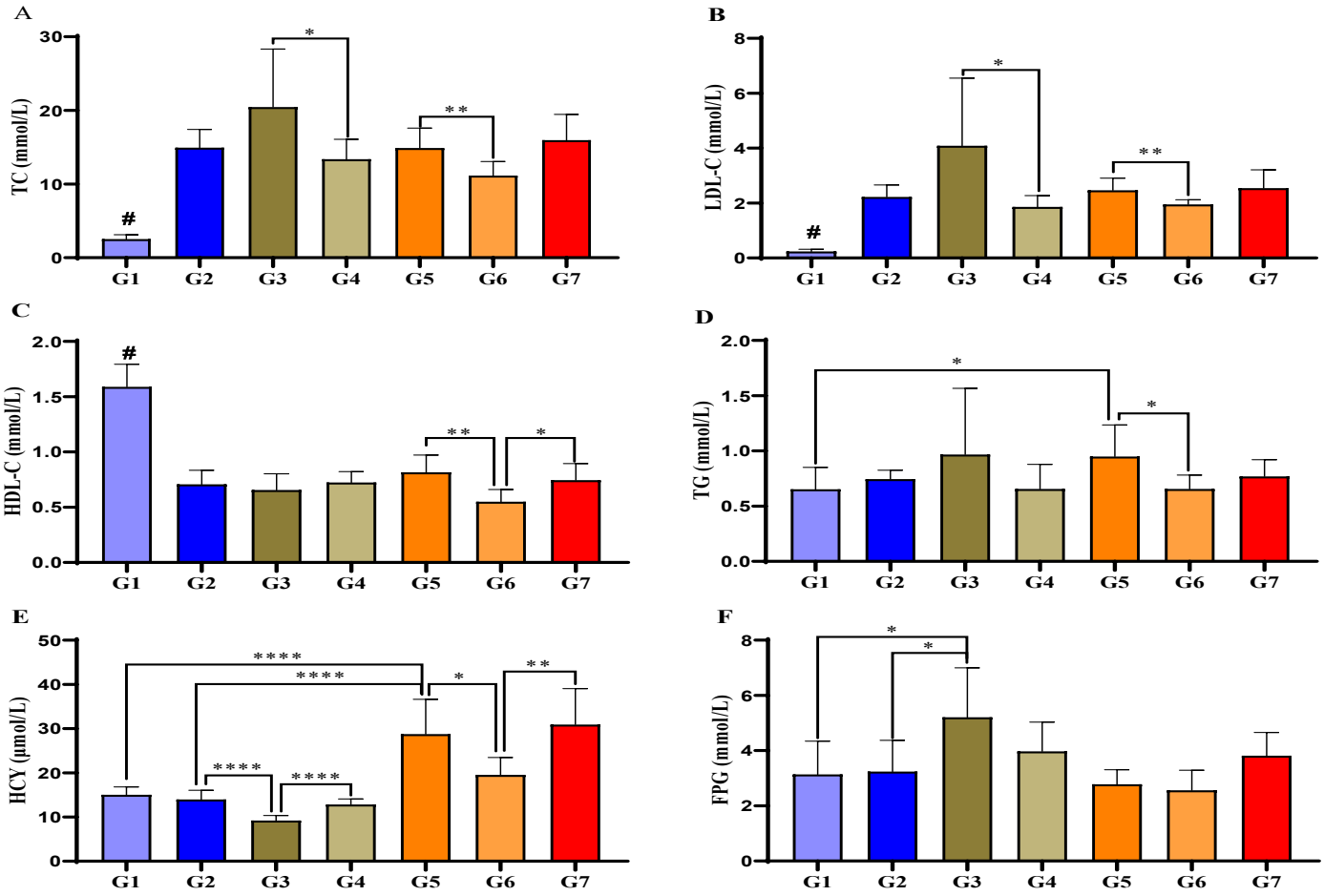
Supplementary Fig. 1. Spearman correlation analysis. (A, B) Spearman correlation between the methylation levels of cg25953130 and the expression of ARID5B in the CAD and control groups. (C) Spearman correlation between Hcy levels and the expression of CCR2 on classical monocytes in the control group. (D) Spearman correlation between HDL-C levels and the expression of CCR2 on classical monocytes in the CAD group.

Abbreviations: m1, classical monocytes; Con, control.



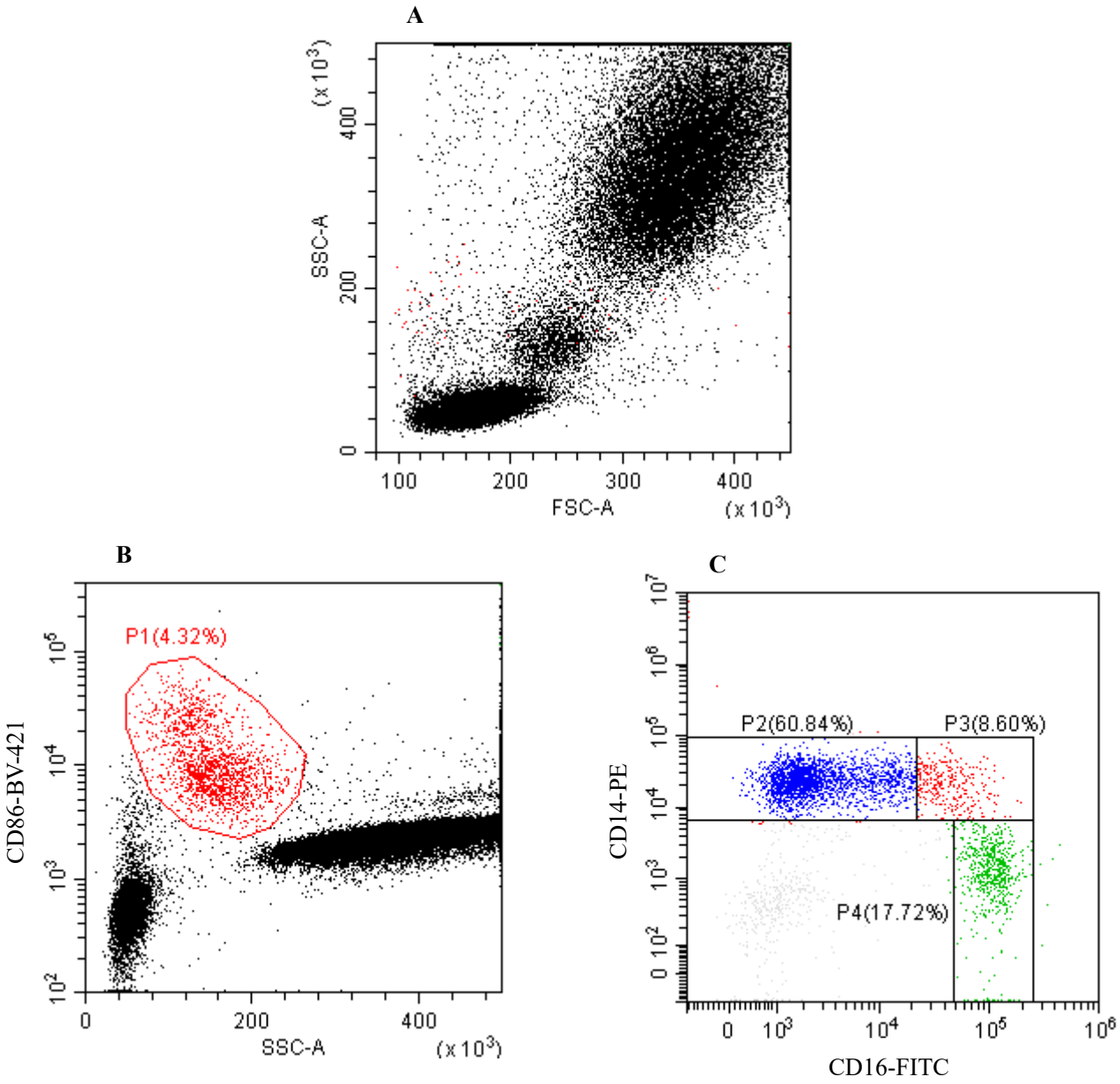
Supplementary Fig. 2. The effects of Hcy, ox-LDL and FA on DNMT1 and ARID5B expression in primary monocytes. (A, B) The effect of folic acid on the expression of DNMT1 and ARID5B in Hcy-treated primary monocytes. (C, D) The effect of folic acid on the expression of DNMT1 and ARID5B in ox-LDL-treated primary monocytes. All plotted values are the mean ± SE values of at least 3 independent experiments.

Abbreviations: FA, folic acid; Hcy, homocysteine; ox-LDL, oxidized low density lipoprotein.
* $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$.

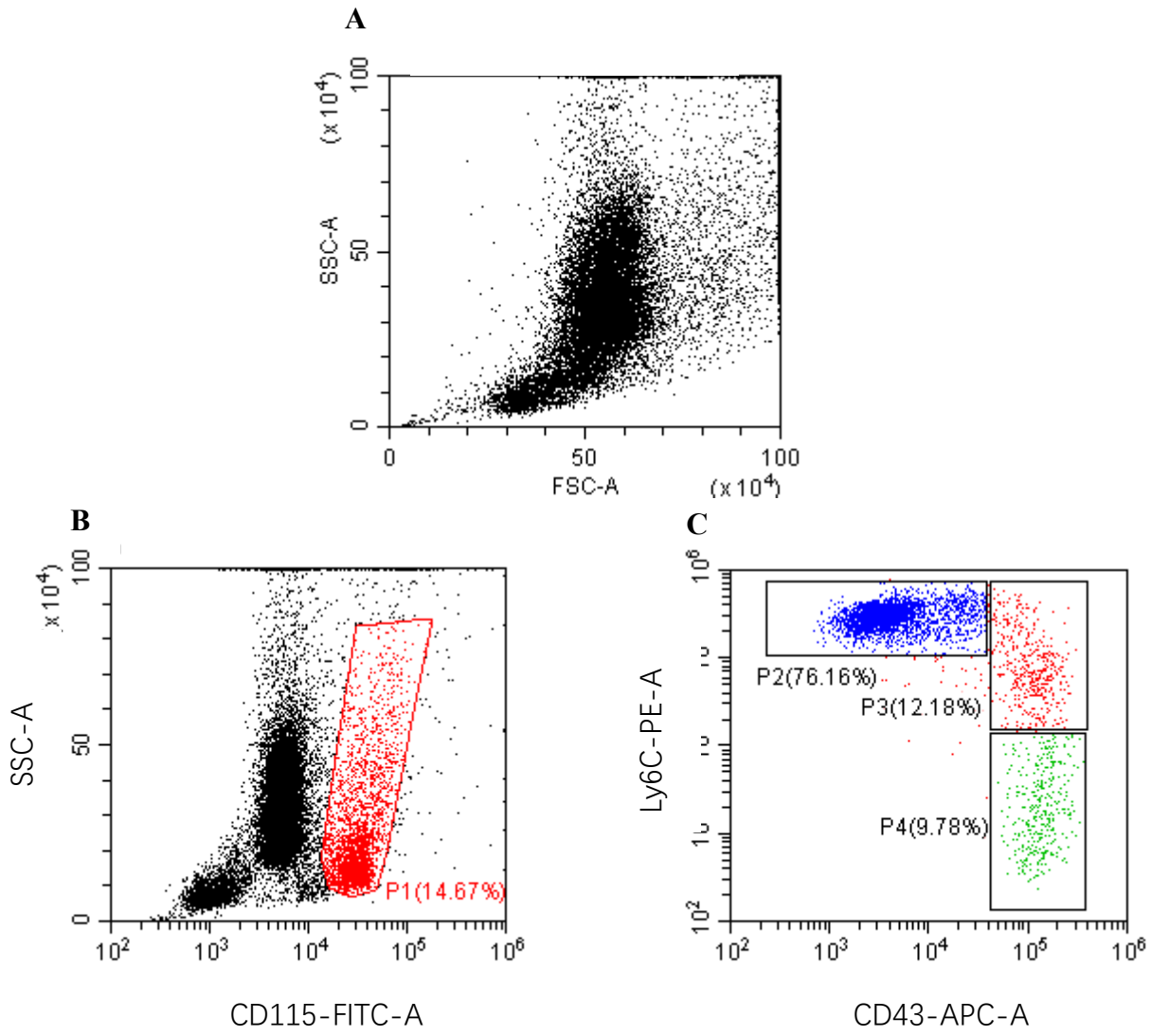


Supplementary Fig. 3. The effect of folic acid on the lipid and Hcy metabolism in mice. (A-D) The effect of folic acid on serum TC, LDL-C, HDL-C and TG in mice. (E) The effect of folic acid on serum Hcy in mice. (F) The effect of folic acid on serum FPG in mice. Mice were divided into seven subgroups: G1, ApoE-WT + ND; G2, ApoE-/- + ND; G3, ApoE-/- + HFD; G4, ApoE-/- + HFD + FA; G5, ApoE-/- + ND + Hcy; G6, ApoE-/- + ND + Hcy + FA; G7, ApoE-/- + HFD + Hcy + FA. Abbreviations: FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; WT, wild type; ND, normal diet; HFD, high fat diet; FA, folic acid.

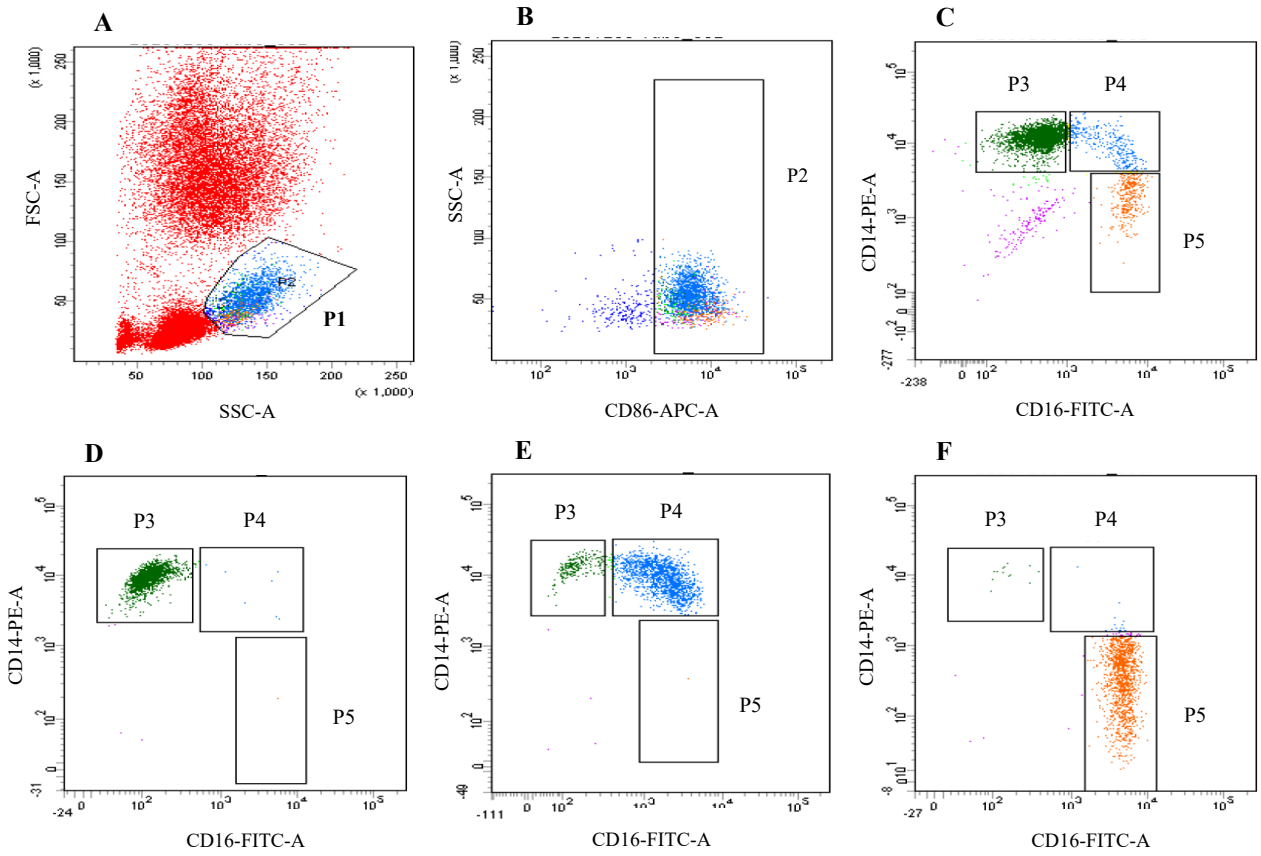
#, the G1 group was statistically different from the other 6 groups; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.



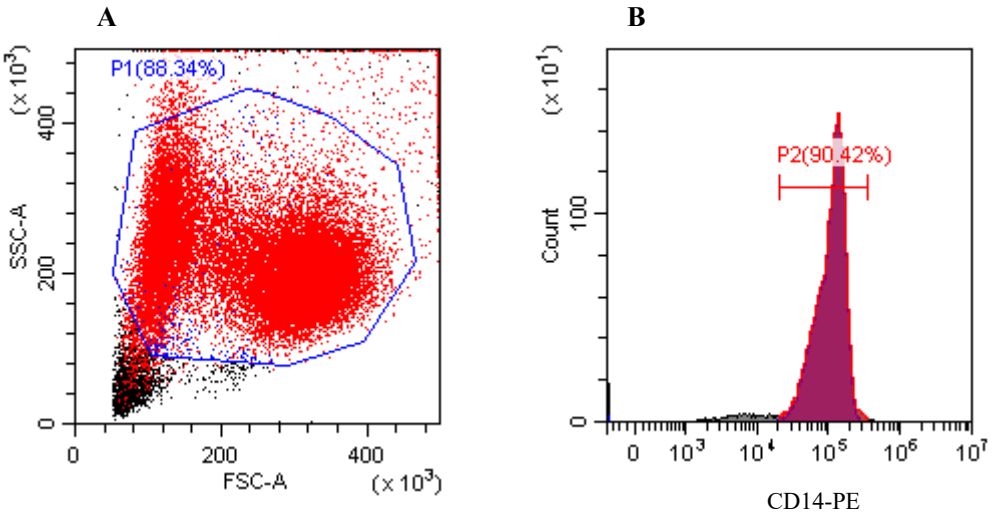
Supplementary Fig. 4. Gating strategy for human monocyte subsets. Circulating leukocytes in FSC/SSC dot plot were presented in supplementary Fig. 4A. In CD86/SSC dot plot, CD86 positive monocytes were firstly gated (P2, B). Subsequently, in the CD14/CD16 dot plot (C), based on the expression of CD14 and CD16, the identified monocytes were divided into classical (P2, CD14++CD16-), intermediate (P3, CD14++CD16+) and nonclassical (P4, CD14+CD16++) subsets.



Supplementary Fig. 5. Gating strategy for mouse monocyte subsets. Circulating mouse leukocytes in FSC/SSC dot plot were presented in supplementary Fig. 5A. In SSC/CD115 dot plot, CD115 positive monocytes were firstly gated (P1, B). Subsequently, in the Ly6C/CD43 dot plot (C), based on the expression of Ly6C and CD43, the identified monocytes were divided into classical (P2, Ly6C++CD43+), intermediate (P3, Ly6C++CD43++) and nonclassical (P4, Ly6C+CD43++) subsets.



Supplementary Fig. 6. Gating strategy for monocyte subsets sorting and purity identification. Circulating monocytes in FSC/SSC dot plot were presented in supplementary Fig. 6A (P1). In CD86/SSC dot plot, CD86 positive monocytes were firstly gated (P2, B). Subsequently, in the CD14/CD16 dot plot, based on the expression of CD14 and CD16 (C), the identified monocytes were divided into classical (P3, CD14++CD16-), intermediate (P4, CD14++CD16+) and nonclassical (P5, CD14+CD16++) subsets. The monocyte subsets obtained by FCM sorting had good purity (D-F).



Supplementary Fig. 7. Purity identification for CD14+ monocytes. Flow cytometry was used to identify the purity of the obtained monocytes labeled with CD14 monoclonal fluorochrome-conjugated antibody. (A) Gating strategy for monocyte CD14+ monocytes. (B) Purity of the CD14+ monocytes.