Supplemental Fig. 1. Inflammatory signals do not induce JMJD8 levels. Mature 3T3-L1 adipocytes were treated with TNFα (10ng/ml), LPS (1ug/ml), and Palmitate (1mM) for 24 hour and assessed by qPCR and immunoblotting analysis.

Supplemental Fig. 2. JMJD8 does not affect adipogenesis. 3T3-L1 cells were infected prior to differentiation with shJmjd8 and control hairpins or GFP and JMJD8 overexpression viruses. On adipogenic day 8, lipid accumulation was assessed by Oil Red O staining (**A, B**), and adipocyte markers were measured by qPCR analysis (**C**). (n = 3, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.).

Supplemental Fig. 3. Knockdown and overexpression efficiency of *Jmjd8* loss- and gain-of-function models in 3T3-L1 adipocytes. (**A, B**) *Jmjd8* mRNA and protein level in 3T3-L1 cells that were infected with shScr vs. shJmjd8 hairpins (n = 3, $p < 0.05$, Student's t-test, mean ± s.e.m.). (**C**) *Jmjd8* mRNA level in 3T3-L1 cells that were infected with gCon vs. gJMJD8 or GFP vs. JMJD8 lentiviruses (n = 3, $p < 0.05$, Student's t-test, mean ± s.e.m.). (**D, E**) *Jmjd8* mRNA and protein level in 3T3-L1 cells that were infected with GFP vs. JMJD8 lentiviruses (n = 3, $p < 0.05$, Student's t-test, mean ± s.e.m.).

Supplemental Fig. 4. Establishment of *Jmjd8*-knockout mice. (**A**) Deleted regions, as shown by Sanger sequencing, of the *Jmjd8*-knockout founder mouse. (**B**) Body weight of WT and *Jmjd8*-KO mice on chow (n = 5 mice, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**C**) Body composition of WT and *Jmjd8*-KO mice on chow (n = 8 mice, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**D**) Tissue weight per body weight of WT and *Jmjd8*-KO mice on chow (n = 4, 3 mice, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.).

Supplemental Fig. 5. Energy homeostasis in *Jmjd8*-KO and WT mice on HFD. VO2 (**A, B**), VCO2 (**C, D**), energy expenditure (**E, F**), locomotor activity (**G, H**), and food consumption (**I**) measurements on WT and *Jmjd8*-KO mice on HFD (n = 8 mice, $p < 0.05$, Student's t-test, mean ± s.e.m.).

Supplemental Fig. 6. Insulin signal transduction is not impaired in non-adipose tissie of *Jmjd8*-KO mice s. Immunoblot of total and phospho-AKT in muscle (**A, B**), liver (**C, D**), and BAT (**E, F**) from WT and *Jmjd8*-KO mice on HFD after IP injection of insulin (10 U/kg, 10 min) (n = 2, 3 mice). Quantification of western blot in (A) ($p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**G**) Pyruvate tolerance test for WT and *Jmjd8*-KO mice on HFD (n = 5 mice, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.).

Supplemental Fig. 7. Generation of adipocyte-specific *Jmjd8* transgenic mice. The *Jmjd8* transgene tagged with the Ty1 epitope was constructed in a pCAG-loxPStopLoxP vector, whose expression is driven by the CAG promoter upon Cre expression. Linearized transgene plasmid was microinjected into fertilized eggs under direct visualization and implanted into the uterus of pseudopregnant female mice. A heterozygous founder was crossed with adiponectin-Cre mice to generate the WT (Tg/+/AdiCre-) and transgenic (Tg/+/AdiCre+) cohort.

Supplemental Fig. 8. Energy homeostasis in Adi-Jmjd8 TG and WT mice is unchanged on HFD. VO2 (**A, B**), VCO2 (**C, D**), energy expenditure (**E, F**), locomotor activity (**G, H**), and food consumption (**I**) measurements on WT and Adi-Jmjd8 TG mice on HFD. (n = 7, 6 mice, $p < 0.05$, Student's t-test, mean ± s.e.m.).

Supplemental Fig. 9. Additional immune gene expression from obese *Jmjd8*-KO and Adi-Jmjd8 TG mice. The qPCR measurement of immune genes in WT and *Jmjd8*-KO mice on HFD (**A**), and in WT and Adi-Jmjd8 TG mice on HFD (**B**). (n = 3, $p < 0.05$, Student's t-test, mean ± s.e.m.).

Supplemental Fig. 10. The proinflammatory action of JMJD8 originates from adipocytes. (**A**) Co-culture of wild-type RAW264.7 macrophages with L1 adipocytes with altered *Jmjd8* levels. WT RAW264.7 macrophages in the Transwell were co-cultured with L1 adipocytes that had *Jmjd8* knocked down (**B**) or overexpressed (**C**) for 24 hours. Shown is the qPCR measurement of inflammatory genes in WT RAW264.7 macrophages from **B** and **C** (n = 3, $p < 0.05$, Student's t-test, mean ± s.e.m.). (**D**) Co-culture of wild-type 3T3-L1 with *Jmjd8* WT vs. KO macrophages. WT 3T3-L1 adipocytes were co-cultured with WT vs. *Jmjd8*-KO macrophages stimulated with LPS (10 ng/ml) or vehicle for 24 hours. (**E**) Shown is the qPCR measurement of inflammatory genes in L1 adipocytes from **D** (n = 3, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**F**) The basal and insulin-stimulated glucose uptake, assessed by a ^{3}H-2-DG assay in L1 adipocytes from D (n = 2, 4, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.).

Supplemental Fig. 11. JMJD8 is not required for the TNFα-stimulated expression of inflammatory gene expression and insulin resistance. Mature 3T3-L1 adipocytes were lentivirally infected with shScr vs. shJmjd8 and were treated with TNFα (5ng/ml) or vehicle for 3 days. Glucose uptake results (**A**) and gene expression analysis of proinflammatory genes (**B**).). (n = 3, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.).

Supplemental Fig. 12. JMJD8 does not affect the NF-κB signaling pathways. (**A**) Immunoblotting of JMJD8 protein from the nuclear and cytosolic fractions of obese WT vs. KO eWAT, and WT vs. Adi-Jmjd8-TG mice (n = 2 mice). (**B, C**) Western blot analysis and quantification of pNF-κB level in *Jmjd8* knockdown or JMJD8 overexpressing 3T3-L1 adipocytes. GAPDH was used as a loading control (n = *2* per genetic manipulation). (**D-G**) Western blot analysis of pNF-κB level with or without LPS (1ug/ml) treatment for 30 min in *Jmjd8* knockdown or JMJD8 overexpressing 3T3-L1 adipocytes. GAPDH was used as a loading control. (**H, I**) HEK293T cells were transfected with DNA plasmids expressing FLAG-JMJD8, HA-IKKβ, and/or HA-IκB, and protein lysates were subjected to immunoprecipitation with anti-FLAG Ab and blotted with anti-HA or anti-FLAG antibodies. (**J, K**) NF-κB-reporter assay was performed in HEK293T cells that were transiently transfected with expression vectors of JMJD8 or control, with or without TNFα (10 ng/ml) treatment for 6 hours or LPS (1ug/ml) for 6 hours (n = 2).

Supplemental Fig. 13. JMJD8 is largely dispensable for IRF3 in mediating inflammatory gene regulation and insulin resistance. (**A**) Basal and insulin-stimulated glucose uptake measured by a ^{3}H-2-DG assay in vehicle or LPS-treated mature 3T3-L1 adipocytes that were infected with control vectors vs. shRNA against JMJD8 (JMJD8 KD), and/or IRF3 overexpressor (IRF3 OE) lentiviruses (n = 2, 4, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**B-D**) qPCR analysis of *Tnf, Il6*, and *Ccl2* in cells from **A** (n = 6, $p < 0.05$, two-way ANOVA with Student's t-test, mean ± s.e.m.). (**E**) Immunoblotting of IRF3 in the soluble and chromatin fraction of *Jmjd8* knockdown or JMJD8 overexpressing 3T3-L1 adipocytes. HSP90 was used as a loading control for the soluble fractionation, and Lamin A/C were used as a loading control for the chromatin fraction. (**F**) Ccl5-reporter assay was performed in HEK293T cells that were transiently transfected with expression vectors of JMJD8 or IRF3, and JMJD8 with IRF3 ($p < 0.05$, Student's t-test, mean ± s.e.m.).

Supplemental Table 1. Up- and down-regulated genes in the *Jmjd8*-KO eWAT

Upregulated genes

Rnase2a	Col4a6	Serpinb2	Rab9b	Cys1	Spink2
Sema5a	Opn3	Mageb18	Tmem151a	D430019H16Rik	
Fam222a	Egln3	Fbxo21	6430573F11Rik	Apcdd1	
Ces1d	Krt19	Ffar4	Thrsp	Cldn22	
Slc1a1	Gm10532	Adgrg2	Cd163	Chil1	
Msln	Myrf	Acsm3	Gjb5	Serpina3b	
Cand2	Hepacam2	Gapt	Eps8l1	2010016I18Rik	
Aff3	Slc2a4	Popdc2	Peg3os	Pck1	
Cfd	Rbp7	Zfp398	Zbtb16	Cyp2ab1	
Xpnpep2	Tead4	Abca6	Zfp366	Tspan8	
Zfp185	Ankrd29	B930092H01Rik	Gsta3	Lrrn4	
Abca8a	Smyd1	Ndrg2	Retnla	Cachd1	
Lama2	Per2	Cbs	Nkain4	Fam13a	
4930412C18Rik	Fgf11	Krt7	Plagl1	Krt8	
Ppm1l	Ms4a1	Bnc1	Alb	Abcg4	
Hcar1	Ppara	Ccdc92	Cybrd1	Slc15a2	
Sesn2	Pgf	Eci3	Fam214a	Padi4	
Car3	Hoxa7	Omd	Pkhd1l1	F5	
8430408G22Rik	Ptch2	Nnat	A330023F24Rik	4732416N19Rik	
Tmem154	Gng7	Peg3	Krt18	Rprml	
Retn	Spock2	Banp	Ankef1	Hspa1b	
D830031N03Rik	Acvr1c	Ppp1r3c	Upk3b	Vstm2b	
Arrdc3	Prg4	Cd226	Igfbp5	Chst4	
Dhtkd1	Ide	Gm19522	Sctr	Hspa1a	
Adrb3	Ano1	Gsta4	Fmo3	Alox15	
Usp13	Acsm5	Col8a2	Lrp2	Retnlg	
Hmgcs2	Slit3	Slc2a13	Morn4	Mycl	
Aox3	Sult1e1	Wnt2b	B3galt2	Cyp2e1	
Mcf2l	Gpm6a	Gdf10	Perp	Chga	
Agt	Sh3d21	Pygo1	Igfbp2	Angptl7	

Downregulated genes

Tpsb2	Cxcl1	Sema4d	H2-M2	H2-Q5	Ubd	Il1rn	Timeless	Mdk	Cep55	Ptpn18
Akr1b7	4931431B13Rik	Ms4a7	Ccl7	Nepn	Oxtr	Slc15a3	Zbtb20	Mcm6	Cdt1	Pacrgl
Snord123	Tph2	Efr3b	Tnfrsf11a	Oasl1	Lrrc25	Stambpl1	Fkbp1b	Ppih	Ckb	
Cck	Plxdc1	Npas4	Milr1	Akr1cl	Gnal	Rn45s	Pop7	Cma1	Mettl1	
Gpr50	AU022793	Fos	Rhov	Tlr1	Ctsk	Spdl1	Fbln7	Foxm1	Gpank1	
Hpx	Pkib	Syngr1	Dlgap5	Pianp	Alpk2	Mmp12	Uhrf1	Ctss	Fblim1	
Pcp4l1	Crisp2	Casq1	Rrm2	Bcl3	Vsig8	Lat2	Hck	Kcnn4	Adssl1	
Mir3082	Cadm1	Ccr5	Mcoln2	Slamf9	Snhg7	Alyref2	C5ar1	Havcr2	Ube2c	
Il13ra2	Zranb3	Cxcl14	Cdca3	Stap1	Junb	Tyrobp	Gins1	Tubb2b	Pirb	
Fosb	Ptx3	Spc24	H2-Q6	Fcgr1	Ms4a4b	Degs2	Gatm	Rasgef1b	Wdhd1	
Pvalb	Fam65c	Clec12a	Lat	Evi2a	Cd44	Orm2	Tpcn2	Gpr176	Gpr65	
Mmp3	Galnt12	Tnfrsf12a	2700099C18Rik	Wisp2	H2-Q9	Nceh1	Npl	Exoc3l4	Camk2a	
Gm5547	Eef1a2	Atp6v0d2	Tuba1c	Itgax	H2-Q7	Ccnb2	Hmga1-rs1	A4galt	Gpr137b	
Snora70	Hpgds	Dusp9	Dpep2	Fen1	Chchd10	3110039I08Rik	Arhgap25	Rab7b	Gpr137b-ps	
Jmjd8	Itgad	Serpinb9b	Clec7a	Fjx1	Msr1	Cd200r4	Acer3	Pik3ap1	Npy1r	
S100a8	Lair1	Bcl2a1b	Eif2s3y	Fam83f	Cd180	Kif2c	Slc6a6	Pstpip1	Cdc20	
Jchain	Rnf128	Tnfrsf13b	Plekhn1	Iqgap3	Cyr61	Mcm5	Cd68	Hmga1	Lcp1	
Il1r2	Olr1	Mir7653	Adam8	Gadd45b	Tfec	Ms4a6d	Stk38l	Cstb	Lilrb4a	
Myh15	Rgs1	Cd300c2	Tm4sf19	C3ar1	Cd200r1	Evl	Casp1	Lgals3	Insl3	
Spp1	Dnmt3aos	Glipr1	Fcgr4	Myo1e	Cd300lb	Tnip3	Rgs18	Aif1	Atp1a4	
Abcb4	Cxcl10	Tk1	Slc37a2	Mstn	AA414768	Cd84	Ddx3y	Lilra5	Samd10	
Trdn	Sel1l3	Ccl3	Gpnmb	Tmem144	2610524H06Rik	Gpr183	Sirpa	Sms	Tlr6	
Cd72	Htr2b	Nptx2	Pramef12	Runx2	5830432E09Rik	Tgif1	Mthfd1l	Dclk3	Gimap3	
Pex5l	Trem2	Lipf	Rab20	Cpa2	Cdca5	Neurl2	Pbk	Cyth4	Hk3	
Dppa3	Ccl2	Saa3	Egr2	Cdkl4	Tlr13	Spc25	Zc3h12d	Cd14	Fam64a	
Comp	9030619P08Rik	Il7r	A630033H20Rik	Plppr4	Apobec1	Mfap2	Pclaf	Fignl1	Egr1	
Ptchd1	Cdk18	Lcn2	Rwdd3	Atf3	Birc5	Plk2	Clec4a2	Ccsap	Cd83	
Cfi	Ccl12	Matk	Stra6l	Plac8	Rasa4	Mrps33	Otop1	Cyba	Fam134b	
Fosl1	Prrx1	Micall2	Cd3g	Lilr4b	Cdkn3	Socs3	Afap1l2	Casp4	Ier5	
Cox6a2	Clec4d	H2-Q8	Mcm10	Gdf15	Mcpt4	Fam83d	Elovl6	Gas2l3	Tspan33	

Supplemental Table 2. Oligonucleotide sequences used in this manuscript

Hairpin	shJmjd8 #1	GCCTGGTTTCTCAGAGGTTAT
Hairpin	shJmjd8 #2	GGTTAACCAGAAGCTAGTTGG
gRNA	gJmjd8-human_F	CACCGGGGCGGCAGGCTCATGGCGC
gRNA	gJmjd8-human_R	AAACGCGCCATGAGCCTGCCGCCCC
gRNA	gIRF3-mouse_F	CACCGCGAAACCGCGGATTTTGCCC
gRNA	gIRF3-mouse_R	AAACGGGCAAAATCCGCGGTTTCGC
qPCR	Cyclophilin_F	GGTGGAGAGCACCAAGACAGA
qPCR	Cyclophilin_R	GCCGGAAGTCGACAATGATG
qPCR	Jmjd8-mouse_F	CGGTCTGCTTTTGCTCTTTG
qPCR	Jmjd8-mouse_R	TGAGTCCTTGCAAGATGACG
qPCR	Jmjd8-human_F	GACAGGTTGCTGGCTTCGTT
qPCR	Jmjd8-human_R	AGGGCAAGTCCACTTTGTGGTA
qPCR	Cxcl1_F	GCCTATCGCCAATGAGC
qPCR	Cxcl1_R	TGGACAATTTTCTGAACCAAG
qPCR	Cxcl10_F	CCAAGTGCTGCCGTCATTTTC
qPCR	Cxcl10_R	TCCCTATGGCCCTCATTCTCA
qPCR	Lcn2_F	TCCTTCAGTTCAGGGGACAG
qPCR	Lcn2_R	CCAGTTCGCCATGGTATTTT
qPCR	Il13ra2_F	CGTACGCATTTGTCAGAGCA
qPCR	Il13ra2_R	AGGTTTCCAAGAGCAGACCA
qPCR	Adgre1_F	TGCATCTAGCAATGGACAGC
qPCR	Adgre1_R	GCCTTCTGGATCCATTTGAA
qPCR	Mmp3_F	CAGACTTGTCCCGTTTCCAT
qPCR	Mmp3_R	GGTGCTGACTGCATCAAAGA
qPCR	Caspase1_F	TCCGCGGTTGAATCCTTTTCAGA
qPCR	Caspase1_R	ACCACAATTGCTGTGTGTGCGCA
qPCR	Il6_F	CTCTGGGAAATCGTGGAAAT
qPCR	Il6_R	CCAGTTTGGTAGCATCCATC
qPCR	Tnfα_F	ATGAGAAGTTCCCAAATGGC

qPCR	Tnfα_R	CTCCACTTGGTGGTTTGCTA
qPCR	Il1β_F	GCAACTGTTCCTGAACTCAACT
qPCR	Il1β_R	ATCTTTTGGGGTCCGTCCAACT
qPCR	Ccl2_F	GGCCTGCTGTTCACAGTTGC
qPCR	Ccl2_R	CCTGCTGCTGGTGATCCTCTT
qPCR	Ccl5_F	ACACCACTCCCTGCTGCTTT
qPCR	Ccl5_R	GACTGCAAGATTGGAGCACTTG
qPCR	Spp1_F	TCACCATTCGGATGAGTCTG
qPCR	Spp1_R	ACTTGTGGCTCTGATGTTCC
qPCR	Ptx3_F	TGGCTGAGACCTCGGATGAC
qPCR	Ptx3_R	GCGAGTTCTCCAGCATGATGA
qPCR	Cxcl13_F	CTGGAAGCCCATTACACAAAC
qPCR	Cxcl13_R	GGGGAGTTGAAGACAGACTT
qPCR	Asc_F	CAGAGTACAGCCAGAACAGGACAC
qPCR	Asc_R	GTGGTCTCTGCACGAACTGCCTG
qPCR	Nlrp3_F	TGCTCTTCACTGCTATCAAGCCCT
qPCR	Nlrp3_R	ACAAGCCTTTGCTCCAGACCCTAT
qPCR	Cd68_F	AGGGTGGAAGAAAGGTAAAGC
qPCR	Cd68_R	AGAGCAGGTCAAGGTGAACAG
qPCR	Mgl2_F	TTAGCCAATGTGCTTAGCTGG
qPCR	Mgl2_R	GGCCTCCAATTCTTGAAACCT
qPCR	Jmjd4_F	CCTCAAGGACTGGCATCTGT
qPCR	Jmjd4_R	GGACGTCCCAGAACTCATTC
qPCR	Jmjd5_F	CTAGTTCCTGGGAGGCCTGT
qPCR	Jmjd5_R	TGTACCTTGAGCCCACTTCC
qPCR	Jmjd6_F	CCCCTTACAGGTGGTTTGTG
qPCR	Jmjd6_R	GGTCGATGTGAATCCCAGTT
qPCR	Jmjd7_F	CCACTGATGAGGCTGGAACT
qPCR	Jmjd7_R	GCTCCTTTGGTCCTTCTTCC
qPCR	Jmjd8_F	ACTTCACTGAGTGGGCATCC
qPCR	Jmjd8_R	GCTGACAGGGCTAGAGATGG
qPCR	Flh1_F	GGCAGCTGACCTCTAACCTG
qPCR	Flh1_R	TGAGCAGGTGTCACATTTCC
qPCR	Hspbap1_F	AAATTCTGGGCTTACGCTGA
qPCR	Hspbap1_R	GTCAGACCACACCACCTCCT

qPCR	Mina53_F	GACACACGACTTCCTGCTGA
qPCR	Mina53_R	CAGGCCTGAAGGAGTTTCTG
qPCR	No66_F	CACCAAGCTGAATGTCAGGA
qPCR	No66_R	GGTGAGGTGTAGGGAGTGGA
qPCR	Glut4_F	TCATTGTCGGCATGGGTTT
qPCR	Glut4_R	CGGCAAATAGAAGGAAGACGT
qPCR	Pparg_F	CAAGAATACCAAAGTGCGATCAA
qPCR	Pparg_R	GAGCTGGGTCTTTTCAGAATAATAAG
qPCR	Fabp4_F	AAGGTGAAGAGCATCATAACCCT
qPCR	Fabp4_R	TCACGCCTTTCATAACACATTCC
qPCR	Adipoq_F	TGTTCCTCTTAATCCTGCCCA
qPCR	Adipoq_R	CCAACCTGCACAAGTTCCCTT
qPCR	Leptin_F	GAGACCCCTGTGTCGGTTC
qPCR	Leptin_R	CTGCGTGTGTGAAATGTCATTG
qPCR	Arg1_F	CTCCAAGCCAAAGTCCTTAGAG
qPCR	Arg1_R	AGGAGCTGTCATTAGGGACATC