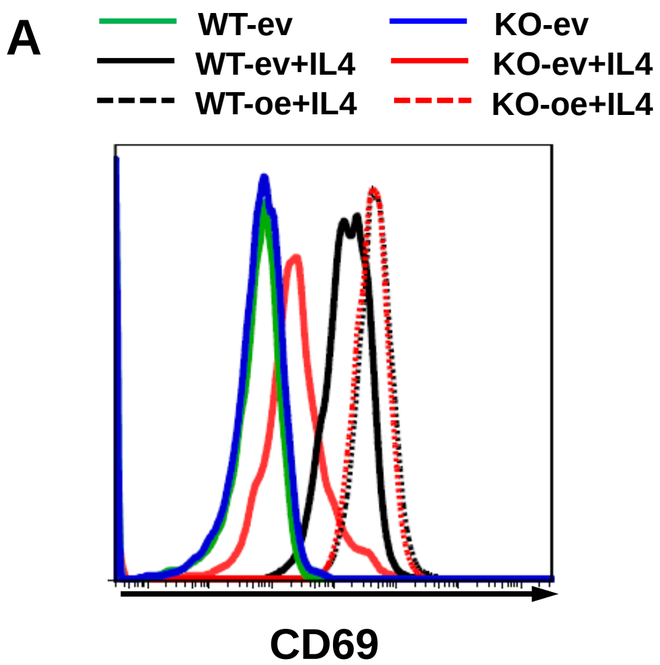

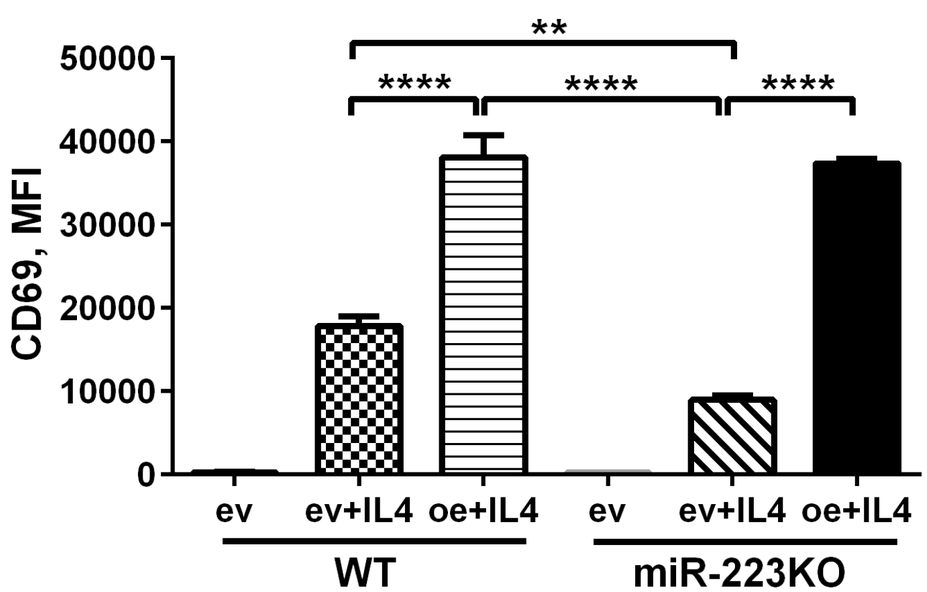

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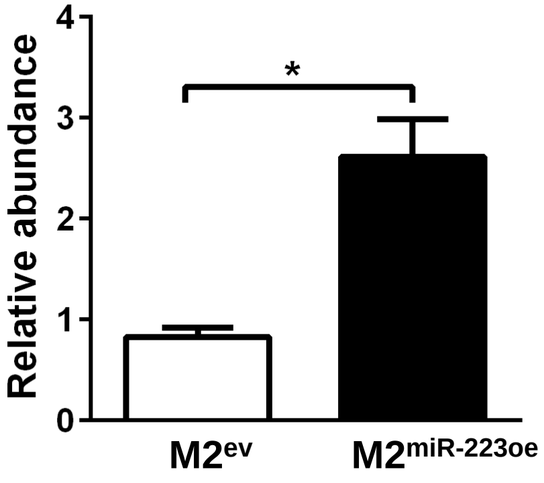
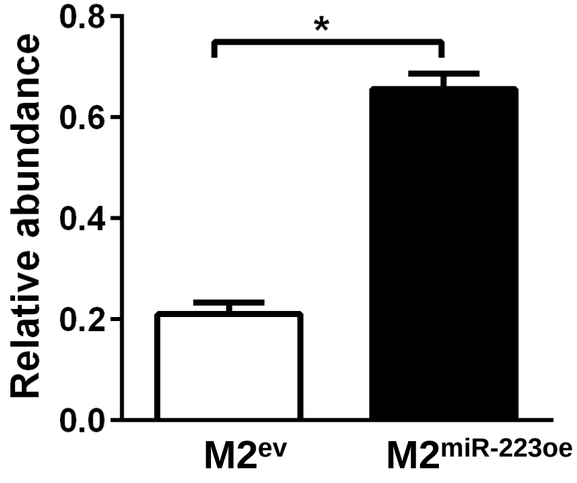
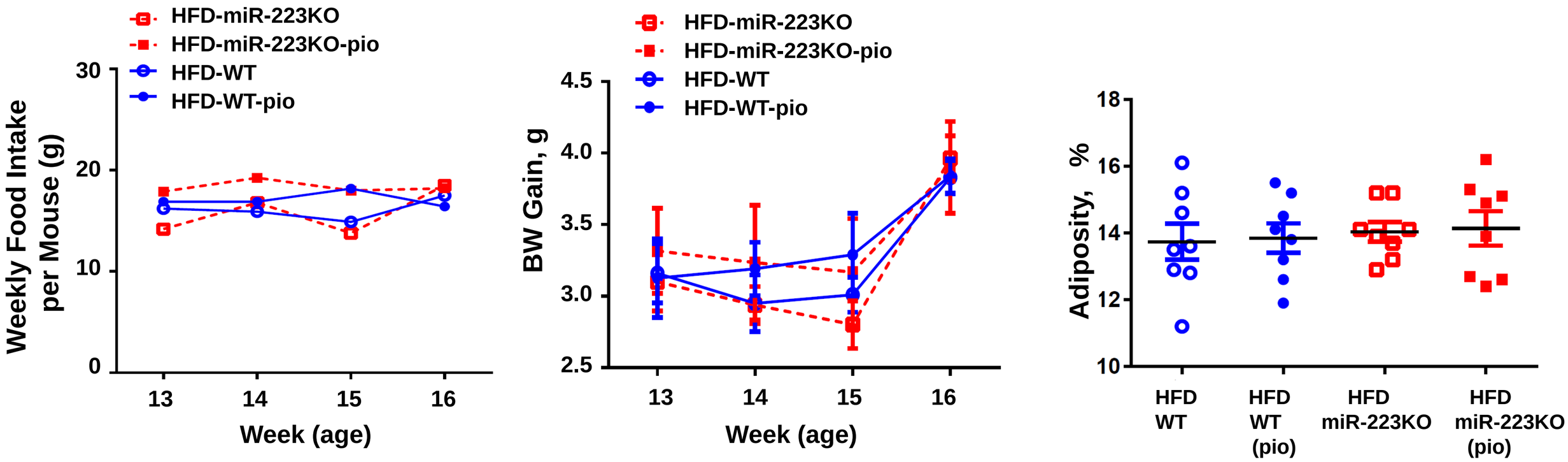
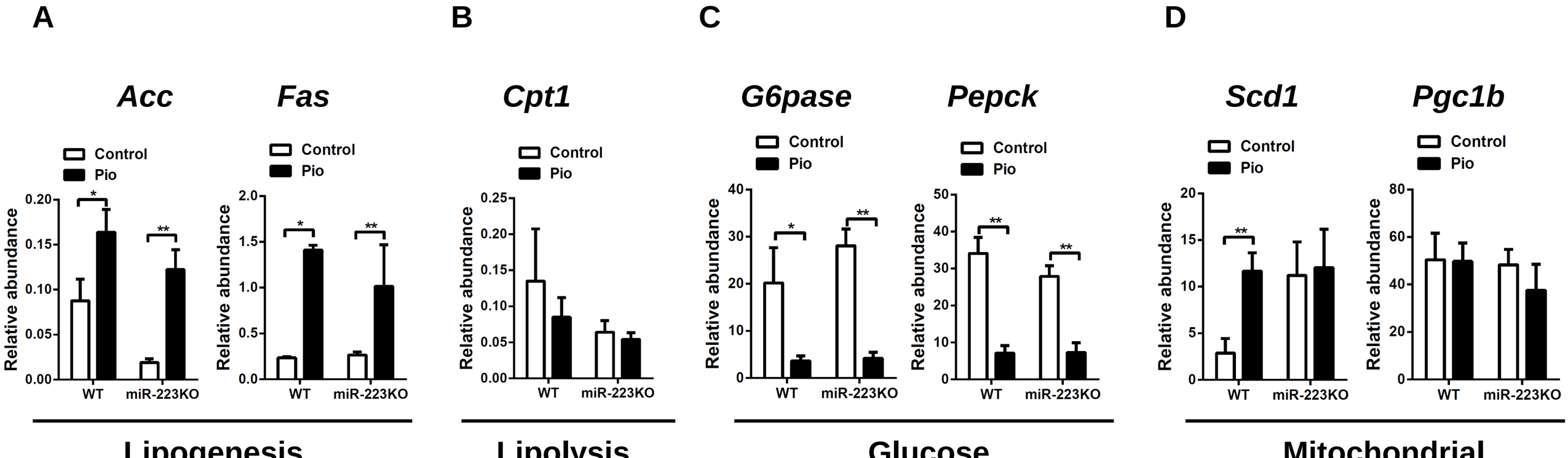




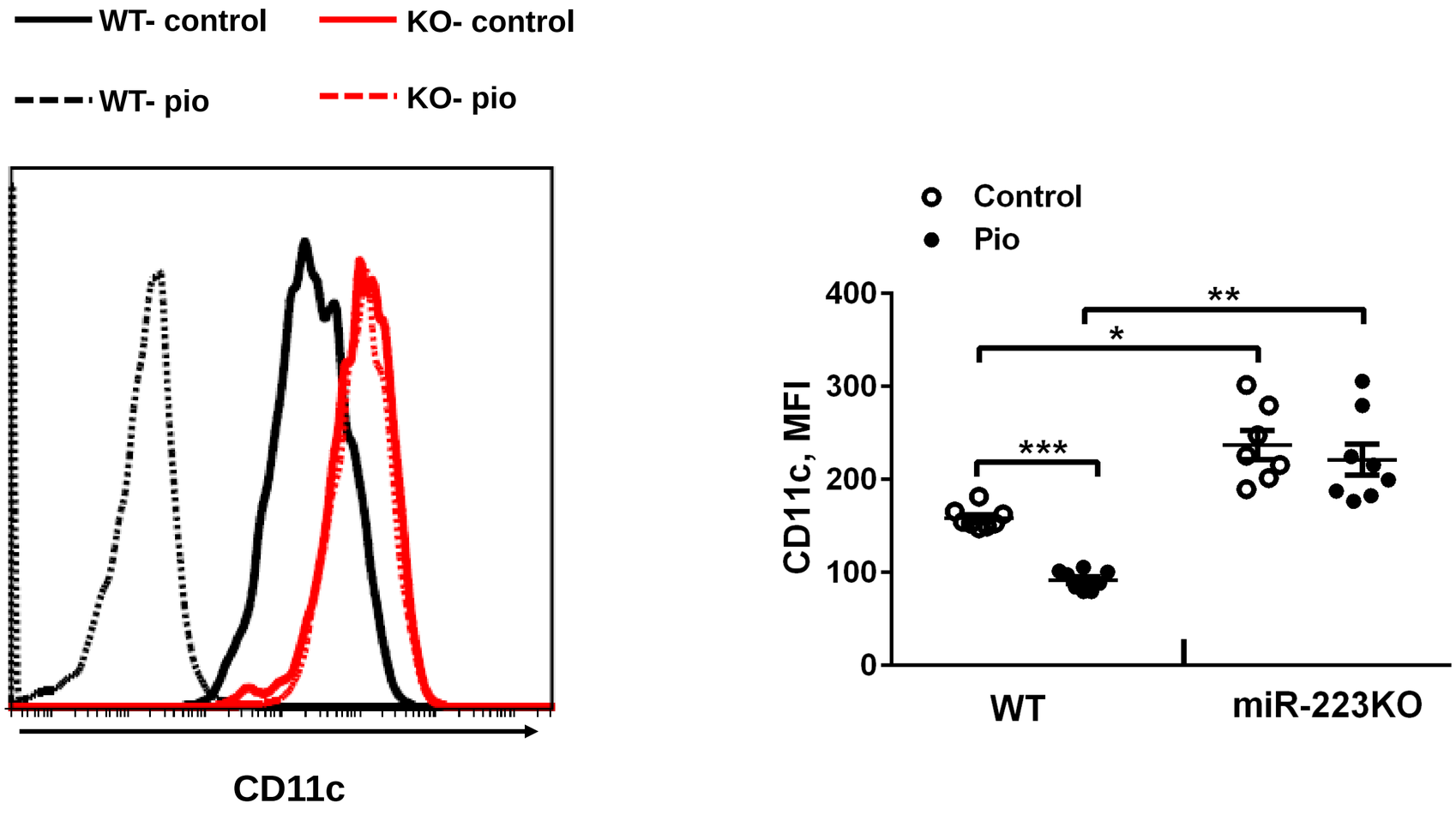
Supplementary Figure S1. Restoring miR-223 rescues the M2 phenotypes of miR-223KO macrophages. **A,** The expression of activation-related cell surface marker CD69 in WT or miR-223KO BMDMs with overexpression of miR-223 in the presence of pioglitazone IL4. ev, BMDMs transfected with empty vector; oe, BMDMs transfected with miR-223 overexpression construct. **B,** The expression of M2 related key genes *Arg1* and *Pgc1a* in miR-223KO BMDMs after introducing miR-223 overexpression construct for 48 hours. n=3.Data are presented as mean ± SEM. **P*<0.05, ***P*<0.01, ****P<0.0001 One-way ANOVA with Bonferroni post-test (a), Student's *t* test (b).



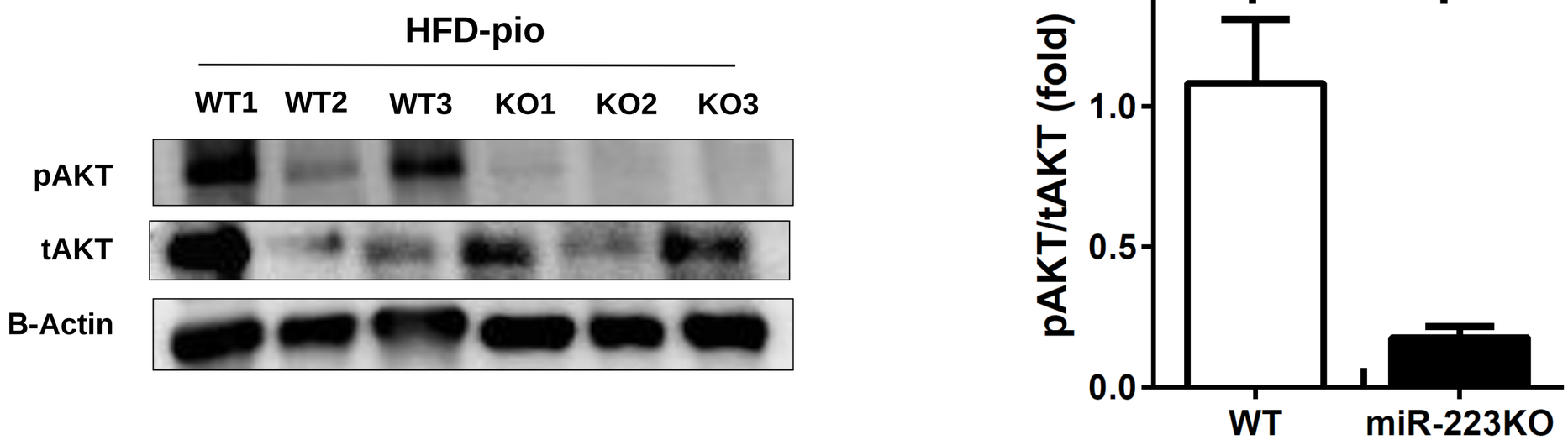
Supplementary Figure S2. pioglitazone treatment does not affect food intake, body weight (BW) gain, and adiposity of HFD-fed mice. Food intake, BW gain, and adiposity of HFD-fed WT or miR-223KO mice were measured during 4-week pioglitazone treatment (n=9-10). Data are presented as mean ± SEM.



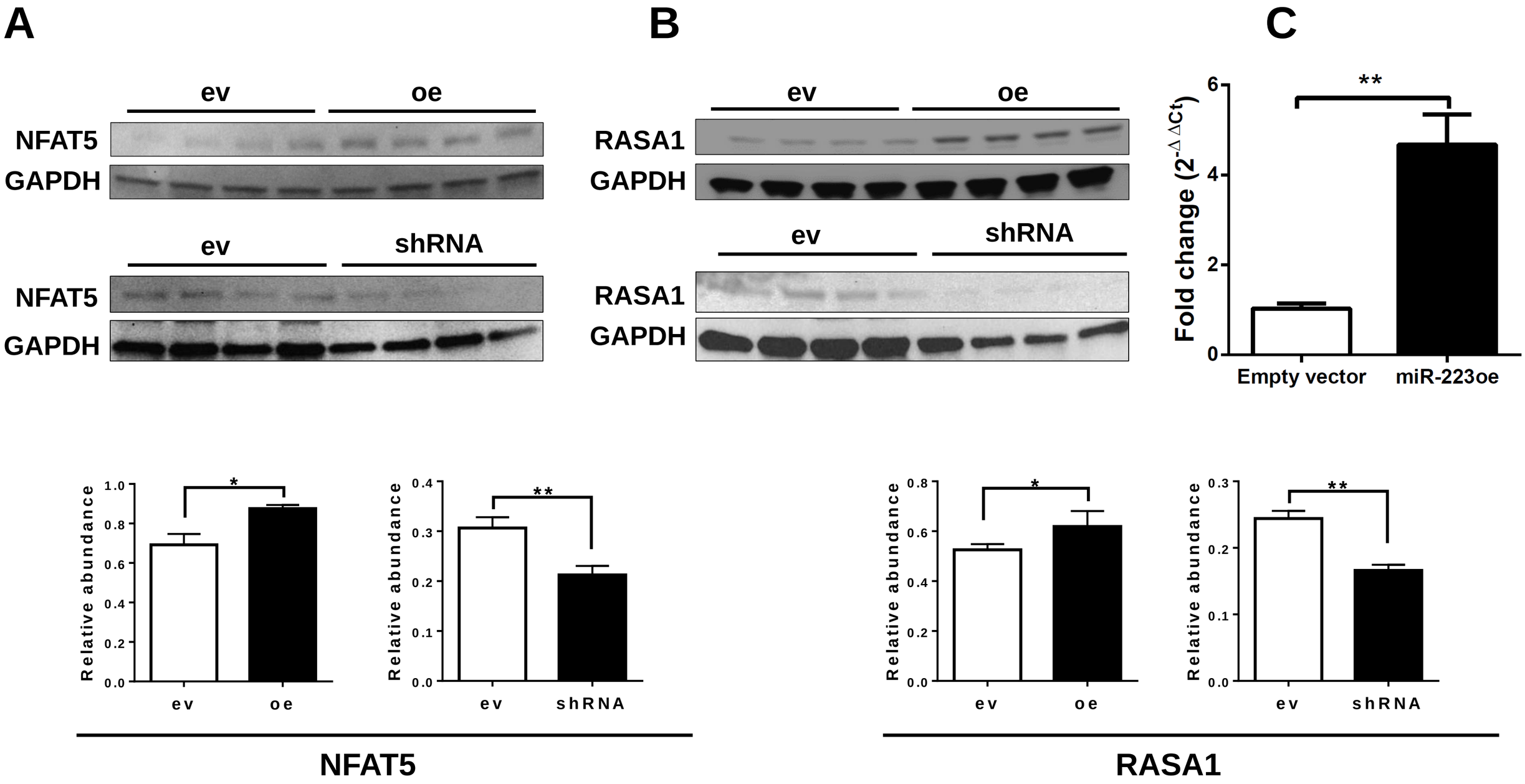
Supplementary Figure S3. The effects of pioglitazone on key genes related to liver metabolic function of HFD-fed WT or miR-223KO mice. The expression of key regulators for lipogenesis (**A**), lipolysis (**B**), glucose metabolism (**C**), mitochondrial function (**D**) was measured in the liver collected from HFD-fed WT or miR-223KO mice without (Control) or with pioglitazone (Pio) administration (normalized to β-actin; n=3). *Acc*, acetyl-CoA carboxylase; *Fas*, fatty acid synthetase; *Scd1*, stearoyl-CoA desaturase-1; *pgc1b*, peroxisome proliferator-activated receptor γ, coactivator 1β; *Cpt1*, carnitine palmitoyltransferase 1; *G6pase*, glucose 6-phosphatase; *Pepck*, phosphoenolpyruvate carboxykinase. Data are means ± SEM. **P*<0.05, **P<0.01 Student's *t* test.



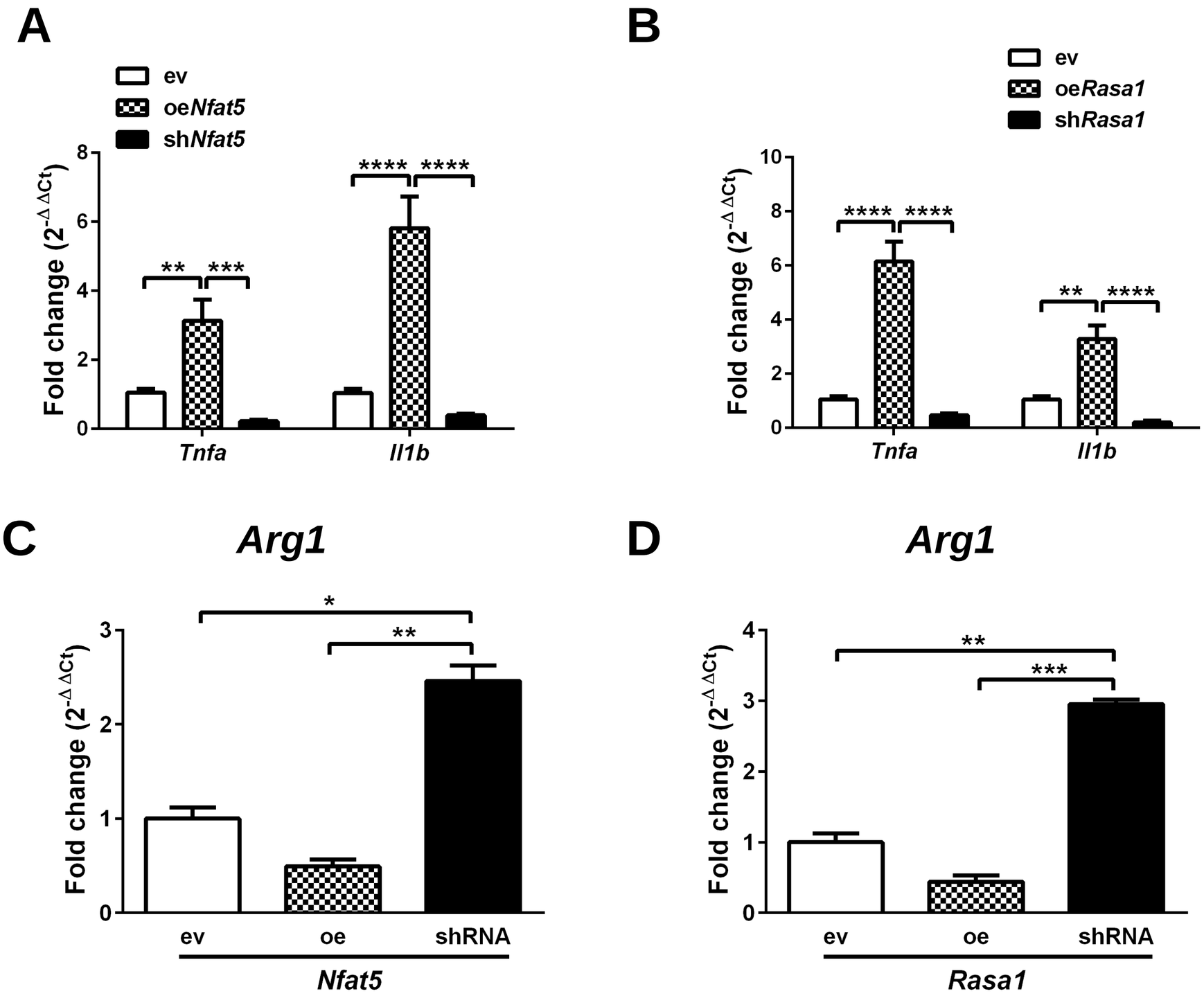
Supplementary Figure S4. The effect of pioglitazone on expression of inflammatory marker CD11c in ATMs. The level of CD11c on the cell surface of F4/80+CD11b+ ATMs in HFD-fed mice was measured by flow cytometry analysis with antibody against CD11c. n=7-9. Data are means ± SEM. *P<0.05, **P<0.01, ***P<0.001 One Way ANOVA with Bonferroni post-test .



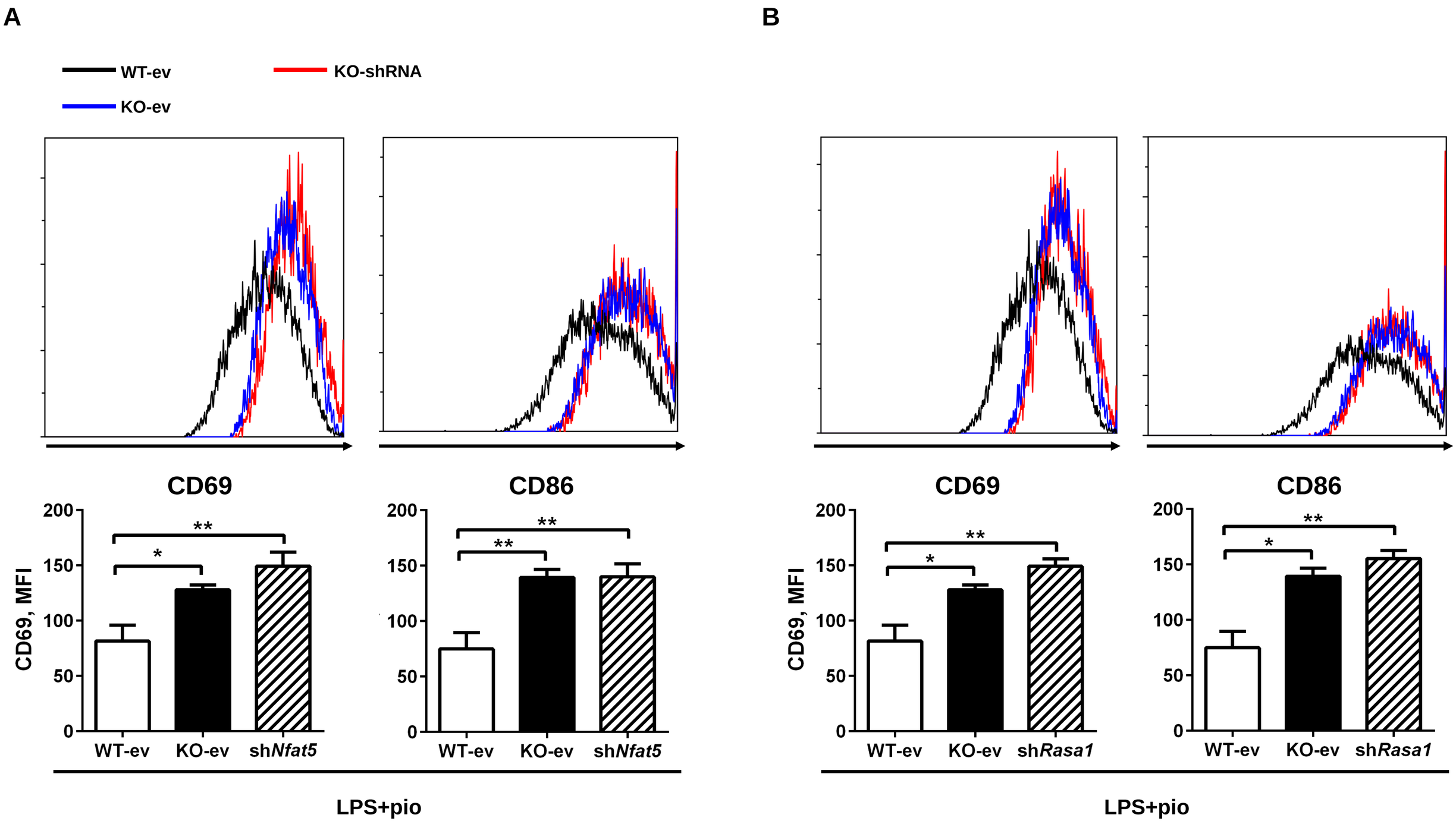
Supplementary Figure S5. The effect of pioglitazone on activation of AKT signaling in visceral adipose tissues (VAT) of HFD-fed WT and miR-223KO mice. The level of AKT activation in VAT of HFD-Fed mice with pioglitazone treatment was measured by western blots with antibodies against phosphorylated AKT (pAKT) and total AKT (tAKT). n=3. Data are means ± SEM. ***P*<0.01, Student's *t* test.



Supplementary Figure S6. The expression level of NFAT5, RASA1, or miR-223 after knockdown or overexpression assay. Overexpression (oe) or knockdown of miR-223 target genes *Nfat5* (**A**) and *Rasa1* (**B**) expression in miR-223KO BMDMs by short hairpin RNA (shRNA) assay were validated by western blots. Cells transfected with empty vectors (ev) were used as control. **C**, The expression of miR-223 was validated by RT-PCR after ectopic expression assay in BMDMs. n=4. Data are means ± SEM. ***P*<0.001, Student's *t* test.



Supplementary Figure S7. The effects of *Nfat5* and *Rasa1* on macrophage activation. *A* and B, The expression of M1 activation-related key genes after knockdown of *Rasa1* or *Nfat5* in miR-223KO BMDMs. n=3. **C and D,** The expression of M2 activation-related gene *Arg1* in miR-223KO BMDMs with knockdown of miR-223 target genes. n=3. Data are means ± SEM. **P*<0.05, ***P*<0.01, ****P*<0.001, ****P<0.0001 One-way ANOVA with Bonferroni post-test .



Supplementary Figure S8. The effect of pioglitazone on M1 activation of macrophages with knockdown of *Nfat5* or *Rasa1*. A and B, The expression of M1 activation-related cell surface marker CD69 and CD86 in BMDMs after knockdown of *Nfat5* or *Rasa1* in the presence of pioglitazone (pio) and LPS. WT-ev, wild type BMDMs transfected with empty vector; KO-ev, miR-223KO BMDMs transfected with empty vector. n=4. Data are presented as mean ± SEM. **P*<0.05, **P<0.01 One-way ANOVA with Bonferroni post-test .