Supplementary Methods

Cell adhesion assays.

Fully differentiated 3T3-L1 adipocytes in 96-well plates were stimulated with mouse recombinant TNF (20 ng/ml) or Palmitate-BSA (250 μM) for 16 h. After washing with serum-free medium, cells were incubated with mouse Fc block (2.5 μg/ml, BD) for 10 min, and then with antibodies to ICAM-1 (20 μg/ml, YN1/1.7.4, BioLegend), VCAM-1 (20 μg/ml, 106, eBioscience) or matched isotype control IgGs (20 μg/ml, BioLegend and eBioscience) for 30 min followed by addition of bone marrow mononuclear cells (BMM). BMM were isolated from C57BL/6 mice or from $Cre^{-}\alpha_4^{f/f}$ and $Cre^{+}\alpha_4^{f/f}$ mice [2 weeks after induction of Cre recombinase with poly-(I:C); poly-(I:C) was administered to both Cre^{-} and Cre^{+} mice] by Histopaque 1077 (Sigma Aldrich). BMM were labeled with BCECF-AM (Invitrogen) for 15 min at 37°C, washed twice with RPMI with 0.1% BSA and then BMM ($1–2 \times 10^4$) were added onto 3T3-L1 adipocytes in RPMI with 0.1% BSA. Cells were allowed to adhere to adipocytes for 30 min at 37°C and then the plate was washed twice. Fluorescence intensity before and after the washings was determined by using a microplate reader (BioTek) and the percentage of adherent cells was calculated as fluorescence intensity of adherent cells / fluorescence intensity of input cells × 100.

Macrophage activation studies.

Peritoneal macrophages were harvested after mouse euthanasia by flushing the peritoneal cavities of C57BL/6 mice, or of $Cre^{-}\alpha_4^{f/f}$ and $Cre^{+}\alpha_4^{f/f}$ mice with 5 ml buffer (PBS+0.5% BSA). Then the cells were incubated with Fc block (BD) and stained with anti-CD45 (30-F11, BD), anti-CD3 (145-2C11, eBioscience), anti-CD11b (M1/70, Biolegend), and anti-F4/80 (BM8, eBioscience) for 20 min at 4°C, and macrophages were FACS-sorted as $CD45^{+}CD3^{-}CD11b^{+}F4/80^{+}$ cells in a FACS Aria II cell sorter (BD). Thereafter, the isolated macrophages were seeded on 48-well plates that were pre-coated with VCAM-1-Fc (10 μg/ml, R&D) or control IgG1 Fc (10 μg/ml, R&D) or onto plates with differentiated 3T3-L1 adipocytes in the absence or presence of the α_4-inhibitor (ELND002; 1 nM) for 6 or 12 h. In some experiments, a second α_4-inhibitor was used (BIO5192 from APExBIO), which provided similar results (data not shown). After incubation, cells were harvested, stained for CD45, CD11b and F4/80 or only CD11b and F4/80 and subsequently fixed-permeabilized with Foxp3 staining kit (eBioscience) and stained with an anti-TNF antibody (MP6-XT22, Biolegend). The expression of TNF was analyzed in a FACS Canto II flow cytometer by using the FACSDiva 6.1.3 software (BD).

Adipocyte-macrophage interactions in the human system.

Human subcutaneous pre-adipocytes (Lonza) were maintained and differentiated to adipocytes according to manufacturer's instructions. At day 10 after starting differentiation, cells were treated with human TNF (10 ng/ml, R&D) or palmitate (250 μM) for 12 h and *VCAM1* expression was analyzed by qPCR.

For cell adhesion assays, peripheral blood mononuclear cells (PBMCs) were isolated from healthy volunteers (after informed consent; the procedure was approved by the Ethics Committee of the Technische Universität Dresden) by density gradient centrifugation (Histopaque 1077, Sigma) and monocytes[1] were separated by using the human monocyte isolation kit II (Miltenyi Biotec) according to manufacturer's instructions. Isolated monocytes were seeded in 12-well plates (5×10^5 cells/ well) and were grown in RPMI-1640 supplemented with 10% FBS, glutamax, penicillin-streptomycin, and recombinant human M-CSF (20 ng/ml, R&D) for 7 days. The cells were then treated with LPS (100 ng/ml, Invivogen) and human IFN-γ (20 ng/ml, BioLegend) for 12 h, in order to acquire an inflammatory M1-like macrophage phenotype[2]. After trypsinization and washing with PBS, the cells were incubated with BCECF-AM for 15 min at 37°C, washed twice with RPMI including 0.1% BSA and then 10^4 cells were added onto differentiated human adipocytes in 96-well plates, pre-treated overnight with TNF (10 ng/ml, R&D). The human inflammatory macrophages were allowed to adhere to adipocytes for 15 min at 37°C in the absence or presence of the α_4-inhibitor (1 nM) and then the plate was washed twice. Fluorescence intensity before and after the washings was determined by using a microplate reader (BioTek) and the percentage of adherent cells was calculated as fluorescence intensity of adherent cells / fluorescence intensity of input cells × 100.

In other experiments, adipocytes in 24-well plates were differentiated for 10 days, and subsequently co-cultured with macrophages that were pre-treated with LPS and human IFN-γ for 12 h, as described above. Before co-culturing, the human adipocytes were pre-treated with T3 (10 nM) and norepinephrine (1 μM) for 3 h to induce a thermogenic response, washed and then co-cultured without or with M1-like macrophages (5×10^4 cells) in the same well for 1 h. The experiments were performed in the absence or presence of a α_4-inhibitor. For mRNA detection of *UCP1* in adipocytes after co-cultures, cells were harvested by trypsinization and washed with PBS. The adipocytes were collected as CD45-negative cells by performing human CD45 negative selection using MACS magnetic beads (Miltenyi). After isolation of RNA, cDNA synthesis and qPCR were performed as described under "Real time PCR".

Immunoblot.

Fat tissues were snap frozen in liquid nitrogen and homogenized by using the T10 basic Ultra-Turrax Homogenizer (IKA) in lysis buffer (150 mM NaCl, 1% Triton X-100, 0.5% sodium deoxycholate, 0.1% SDS, 50 mM Tris-HCl, pH 7.5) containing a protease and phosphatase inhibitor cocktail (Roche). After centrifugations, separation on SDS-PAGE gels and transfer to PVDF membrane, immunoblotting was performed with primary antibodies against UCP1 (Abcam; catalog # ab10983), vinculin (Cell Signaling; catalog # 4650) or actin (Santa Cruz Biotechnology; catalog # sc-1616-R). After incubation with secondary HRP-conjugated antibody (R&D), proteins were detected by using the SuperSignal West Pico Chemiluminescent substrate (Thermo Scientific).

Real-time PCR.

White and brown fat tissues were snap frozen in liquid nitrogen. The samples were homogenized by using the Precellys 24 beads in Trizol (Invitrogen) and total RNA was isolated. In addition, RNA from cell cultures or from cells isolated from fat tissues was also extracted by using Trizol. RNA was reverse-transcribed with the iScript cDNA Synthesis Kit (BioRad). qPCR was performed by using the SsoFast EvaGreen Supermix (BioRad) and gene-specific primers (**Supplementary Table 1** for mouse primers **and Supplementary Table 2** for human primers used in Fig. 7h and 7j) in a CFX384 Real time PCR detection system (BioRad). Relative mRNA expression was calculated according to the ΔΔCt method[3] upon normalization to *18S* [4, 5] or *ACTB*.

Supplementary Tables

gene <mouse>	sequence 5' to 3' - for	sequence 5' to 3' - rev
Vcam1	CTTCCCAGAACCCTTCTCAG	GGGACCATTCCAGTCACTTC
Ucp1	GTGAAGGTCAGAATGCAAGC	AGGGCCCCCTTCATGAGGTC
Cidea	CTCGGCTGTCTCAATGTCAA	GGAACTGTCCCGTCATCTGT
Cox8b	TGTGGGGATCTCAGCCATAGT	AGTGGGCTAAGACCCATCCTG
Cox7a1	CAGCGTCATGGTCAGTCTGT	AGAAAACCGTGTGGCAGAGA
Acsl1	TCCTACAAAGAGGTGGCAGAACT	GGCTTGAACCCCTTCTGGAT
Prdm16	TGAGCCCCAAGGAGTCTATG	GACGAGGGTCCTGTGATGTT
Dio2	CAGTGTGGTGCACGTCTCCAATC	TGAACCAAAGTTGACCACCAG
Elovl3	TCCGCGTTCTCATGTAGGTCT	GGACCTGATGCAACCCTATGA
Ppargc1a	ATACCGCAAAGAGCACGAGAA	CTCAAGAGCAGCGAAAGCGTCACA
Ntn1	CTCAGTGGTTACATACAG	CTCCTCATTTCAGTCTTG
Rn18s	GTTCCGACCATAAACGATGCC	TGGTGGTGCCCTTCCGTCAAT

Supplementary Table 1: qPCR Primer sequences (mouse).

gene <human>	sequence 5' to 3' - for	sequence 5' to 3' - rev
UCP1	GTGTGCCCAACTGTGCAATG	CCAGGATCCAAGTCGCAAGA
ACTB	GCTGTGCTACGTCGCCCTG	GGAGGAGCTGGAAGCAGCC
VCAM1	ATGCCTGGGAAGATGGTCG	GACGGAGTCACCAATCTGAGC

Supplementary Table 2: qPCR Primer sequences (human).

References

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