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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Ct values for qRT-PCR data were calculated by Stepone software (version2.1; Applied Biosciences). Histology images were photographed by Nano Zoomer digital pathology (Hamamaszu).
Data analysis	We used Microsoft Excel and Graphpad Prism for statistical analyses. For flow cytometry data analysis, we used FlowJo (Treestar). Histology images were analyzed by imageJ software.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

All data that support the findings of this study are included in the main and supplementary figures and supplementary table 1. Uncropped Western blot data is presented in Supplementary Fig. 7-8.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was estimated by pilot experiments that showed trends of effects and their sizes as well as previous experience for the similar experiments.
Data exclusions	Mice were excluded when showing poor body condition such severe dermatitis or weight loss after high fat diet or surgery, since body weight change or severe inflammation and stress out of dermatitis or post-opt trauma can profoundly affect glucose and lipid metabolism.
Replication	We considered all replications were successful, if similar results were obtained from at least 2 independent experiments.
Randomization	Mice were randomly allocated to groups (e.g. NCD vs HFD groups). Since female mice are resistant to HFD-induced weight gain and insulin resistance, only criteria were sex and age.
Blinding	No blinding was performed. Since mice or samples were randomly allocated in all assays, while no blinding was performed, experimenters were barely able to distinguish the groups during performing the assays.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☒	☐ Unique materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☐	☒ Research animals
☐	☒ Human research participants

Antibodies

Antibodies used	anti-cleaved caspase-3 (Cell signaling technology, Cat. No. 9664), anti-HIF-1α (Abcam, Cat. No. ab-2185), anti-HIF-2α (Novus Biologicals, Cat. No. NB100-122), anti-HSP90 (Santa Cruz Biotechnology, Cat. No. SC-13119), total OXPHOS rodent WB antibody cocktail (Abcam, ab-110413), anti-Adiponectin (Invitrogen, Cat No. MA1-054), anti-CD45 (eBioscience, Cat No. 83-0451-42), anti-CD11b (eBioscience, Cat No. 11-0112-82), anti-F4/80 (eBioscience, Cat No. 25-4801-82), anti-CD11c (eBioscience, Cat No. 17-0114-82), anti-CD206 (BioLegend, Cat No. 141706), anti-CD3 (eBioscience, Cat No. 56-0032-82), anti-CD4 (eBioscience, Cat No. 17-0041-82), anti-CD8 (BioLegend, Cat No. 100722), anti-Foxp3 (eBioscience, Cat No. 12-5773-80), FITC-labeled anti-Ki-67 monoclonal antibodies (eBioscience, Cat. No. 11-5698-82).
Validation	All the antibodies used in this study were validated through our previous reports, as well as by the providers. For example, according to the manufacturers' website, the anti-cleaved caspase-3, anti-HIF-1α, anti-HIF-2α, anti-HSP90 antibodies, anti-Adiponectin antibodies and the total OXPHOS rodent WB antibody cocktail were validated at least for the use of Western blots with mouse proteins, and the anti-CD45, anti-CD11b , anti-F4/80, anti-CD11c, anti-CD206 , anti-CD3 , anti-CD4, anti-CD8, anti-Foxp3, and FITC-labeled anti-Ki-67 antibodies were validated for the use of flow cytometry analysis of mouse cells.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	3T3-L1 cells were purchased from ATCC
Authentication	3T3-L1 preadipocyte cell line was purchased from ATCC and validated for adipogenic differentiation potential by qRT-PCR and morphologic changes.
Mycoplasma contamination	Negativity for mycoplasma contamination was tested in at least one vial from each passage stock vials. After recovery, experiments were finished within 5 passages. Further testing of mycoplasma contamination was checked every 6 months in all currently cultured cells. All tested cells were mycoplasma free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Research animals

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Animals/animal-derived materials	Ant2fl/fl mouse strain was gifted from Dr. Douglas Wallace laboratory. Ant2fl/fl mice were crossed to mice expressing Cre recombinase (Jackson Labs, strain # 028020) or Cre-ERT2 chimeric protein (Jackson Labs, strain # 025124) under the control of the Adiponectin promoter. Male mice were fed HFD at 7-8 weeks of age for upto 14 weeks or kept on NCD.

Human research participants

Policy information about studies involving human research participants

Population characteristics	MNL, MNO and MAO groups subjected in the current study was in ages of 35+/-4 (3 males and 4 females;), 34+/-2 (1 male and 10 females), 43+/-3 (2 males and 7 females) years old, respectively. Details are available in Methods and Supplementary Table 1.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ Magnetic resonance imaging

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Details are available in Methods
Instrument	FACS CANTO (BD Biosciences) was used for the flow cytometry data acquisition.
Software	Data was analyzed using FlowJo software (Treestar).
Cell population abundance	Sorting was not performed.
Gating strategy	Detailed gating strategy is shown in Supplementary Fig. 4a, 4d, and 4f.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.