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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the 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
☐	☒	A statement on 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 statistical parameters 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

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data were collected with the microplate reader Infinite M200 Pro system (Tecan) using the Magellan 7.1 SP1 software, with the real-time PCR QuantStudio 3 system (Applied Biosystems) using the QuantStudio Design and Analysis v.1.5.2 software, with the iBright CL1500 Imaging System (Invitrogen) using the on-instrument software version 1.8.0, with the LSRFortessa X-20 cell analyzer (Becton Dickinson) using the BD FACSDiva Software Version 8.0 (Build 2013 07 02 02 11) and with the Eclipse Ti-U inverted microscope (Nikon) using the NIS-Elements BR Imaging software version 4.20.03 (Build 995) 64bit.
Data analysis	Data were analyzed with GraphPad Prism 9 for Windows (GraphPad Software), Microsoft Excel 2007 and 2013, FlowJo software version 10.8 (Becton Dickinson), GSEA version 4.3.2 and R open source software (version 4.3.1). Further details are available in the manuscript.

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio 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 description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

No new datasets were generated during the current study. The transcriptomic data analyzed are available from GEO under the accession number GSE130991 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE130991), GSE5099 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE5099), GSE127267 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE127267) and GSE182233 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE182233). The clinical data that support the findings of this study are not publicly available, since they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure data privacy of the study participants. However, they can be applied for through an individual project agreement with Prof. François Pattou (Lille, France). The authors declare that the main data supporting the findings of this study are available within the paper and its supplementary information file. Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was collected based on self-report and considered in the study design as a covariate. Both males and females were included and sex is reported along with other clinical parameters in Supplementary Table 1, 2, 5 and 6. Sex-based analyses were performed and we did not find differences in GDF15 expression or plasma GDF-15 concentration according to sex attribute.
Reporting on race, ethnicity, or other socially relevant groupings	Race/ethnicity was not considered in the study design as a covariate and neither as an inclusion nor exclusion criteria.
Population characteristics	All relevant population characteristics for the current study are reported in Supplementary Table 1, 2, 5 and 6.
Recruitment	Patients enrolled in the present study were participants of the Biological Atlas of Severe Obesity (Atlas Biologique de l'Obesité Sévère [ABOS]) cohort and were recruited at the Centre Hospitalier Universitaire de Lille (France). Eligibility criteria are detailed in ClinicalTrials.gov (NCT01129297). For the confirmation cohort, patients were recruited at the University Hospital of Liège (Belgium).
Ethics oversight	All procedures were ethically approved by the Comité de Protection des Personnes Nord Ouest IV and were compliant to the French National Ethics Committee guidelines. Written informed consent was obtained from all participants. For the confirmation cohort, all procedures were approved by the ethics Committee of Liège University Hospital. Written informed consent was also obtained from all participants. The analysis performed in this study aligned with the original scopes and objectives of the ABOS and Liège cohort studies and no additional ethic approval was therefore requested.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	No statistical methods were used to pre-determine the sample size. Instead, sample size was chosen based on previous experience or literature and by taking into consideration the biological and technical variance of the investigated parameters. The exact number of biological replicates is specified for each experiment in the corresponding figure legend.
Data exclusions	For in vitro studies, no data were excluded. For in vivo studies in mice, one plasma sample was lost (Fig. 2L) and one data was excluded due to the contamination of ingAT by lymph node (Fig. 5A & Supplementary Fig. 5E). For translational research in human, one data was excluded due to the low RNA quality of one sample after cell sorting (Fig. 4C & Supplementary Fig. 4C). These data are indicated by NA or * in the Source Data. Importantly, the complete removal of the few biological units with any missing or excluded data does not impact the conclusions draw in the study, but were kept for increasing statistical power.
Replication	Most effects reported in this study were observed repeatedly. For in vitro studies, between 4 and 8 independent experiments were performed. For mouse studies, 6 to 12 mice per experimental group were assigned. For human studies, 12 to 23 individuals per experimental group were selected and some key findings, such as the increased expression of GDF15 in visceral adipose tissue from patients with obesity,

	were confirmed in a second cohort. The exact number of biological replicates is specified for each experiment in the corresponding figure legend.
Randomization	Mice were randomized and allocated to the different treatment groups based on body weight and in some experiments based on body weight and plasma GDF-15 concentrations.
Blinding	Investigators were blinded whenever possible for data collection and analysis. Complete blinding was not always realistic because some treatments induced an obvious phenotype (HFD-induced obesity) or because preparation of reagents and delivery was made by the same operator (in vitro study).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Antibodies used for macrophage depletion, western blot and histology are reported in Methods section. Antibodies used for cell sorting and flow cytometry are provided in Supplementary Table 8. Antibodies description in manuscript includes names, supplier names, catalog numbers and clone numbers.
Validation	The anti-GDF15 antibody (Novus cat#NBP2-44214, clone 6D12.H10.E4) was validated for western blot application using BMDM from Gdf15 KO mice (Source data Fig. 3H). Other antibodies used in the study have been validated by suppliers, other groups or our lab for the species and applications. All commercial antibodies have been tested for specificity by their respective suppliers.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	RAW 264.7 mouse macrophage cell line was obtained from ATCC (cat#TIB-71) and was established from a tumor in a male mouse. Immortalized human hepatocytes (IHHs) were provided by Pr. Folkert Kuipers (Groningen, The Netherlands), who generated this cell line from a healthy liver of man (DOI:10.1023/a:1007404028681).
Authentication	RAW 264.7 and IHHs were not authenticated but displayed typical characteristics of macrophage (morphology, cytokines production) and hepatocyte (morphology, size, albumin expression), respectively.
Mycoplasma contamination	Cell culture samples were regularly tested and confirmed negative for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Eight-week old male C57BL/6J mice were purchased from Charles River Laboratories. Animals were maintained at 22°C ± 2°C on a 12-h light/dark cycle with ad libitum access to food and water in specific pathogen-free animal facilities (Pasteur Institute of Lille PLEHTA or University of Lille EOPS2).
Wild animals	The study did not involve wild animals.
Reporting on sex	Mouse experiments were performed on males as females developed less severe obesity and metabolic diseases than males upon HFD-feeding.

Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal procedures were performed in accordance with European guidelines on the protection of animals used for scientific purposes (2010/63/UE) and approved by the ethical committee for animal experimentation of the Nord-Pas-de-Calais Region (CEEA75) under the following numbers: APAFIS#7738-2015121713177853, APAFIS#7160-2017040313471173, APAFIS#2017040313241087, APAFIS#11237-2017091112285145 and APAFIS#30876-2021040112094087.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

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	Tissues were collected in PBS and kept on ice until processing, except for AT which has been kept at RT when adipocytes were also collected as described in adipocyte and SVF separation section. Blood was collected in EDTA blood collection tubes and kept on ice until red blood cells lysis step. Spleen was gently pressed on a 70 µm cell strainer by using the flat end of a 1 mL syringe plunger. Other tissues were minced with scissors and digested in DMEM containing 1 mg/mL collagenase D (Roche cat#11088882001) and 0.1 mg/mL of DNAse I (Roche cat#10104159001) at 37 °C under agitation for 30 min for AT, 45 min for liver and 60 min for lung. Cell suspension was passed five to ten times through a 10 ml syringe with 18 G needle (19 G needle used for liver) and then through a 70 µm cell strainer (100 µm used for AT). After centrifugation, red blood cells were lysed by incubation in ammonium chloride-based buffer. Cells were blocked by using a combination of anti-CD16/CD32 (clone 2.4G2) (BD Biosciences, cat#553142) and anti-FcγRIV (clone 9E9) (BioLegend cat#149502).
Instrument	Cell suspensions were run into an Influx cell sorter (Becton Dickinson), a FACS ARIA III cell sorter (Becton Dickinson) or an LSRFortessa X-20 cell analyzer (Becton Dickinson).
Software	Data were collected using the BD FACSDiva Software Version 8.0 (Becton Dickinson) and analyzed using FlowJo software version 10.8 (Becton Dickinson).
Cell population abundance	Percentages of cell populations are illustrated in the manuscript. In cell sorting experiments, cell purity was always >85% and mostly >90%.
Gating strategy	For human VAT, cells were sorted as illustrated in Supplementary Fig. 4A. For mouse epiAT and ingAT, cells were sorted as illustrated in Supplementary Fig. 3A. For mouse blood, the following CD45+ cell populations were sorted: neutrophils (CD11b + Ly6G+), T cells (Ly6G- CD3ε+ TCRβ+), B cells (Ly6G- CD3ε- TCRβ- CD19+) and monocytes (Ly6G- CD3ε- TCRβ- CD19- CD11b+ CD115+). For mouse spleen, the following CD45+ cell populations were sorted: B cells (CD19+ MHCII+), T cells (CD3ε+ TCRβ+ MHCII−), neutrophils (CD3ε− TCRβ− CD19− CD11b+ Ly6G+), macrophages (CD3ε− TCRβ− CD19− Ly6G− F4/80+), monocytes (CD3ε− TCRβ− CD19− Ly6G− F4/80− CD11b+ CD115+) and DCs (CD3ε− TCRβ− CD19− Ly6G− F4/80− CD115− CD11c+ MHCII+). For mouse liver, the following CD45+ cell populations were sorted: T cells (CD3ε+ TCRβ+ CD19− CD20−), B cells (CD19+ CD20+ MHCII+) and macrophages (CD3ε− TCRβ− CD19− CD20− F4/80+ CLEC4F+). For mouse lung, the following CD45+ cell populations were sorted: T cells (CD3ε+ TCRβ+ MHCII−), neutrophils (CD3ε− TCRβ− CD19− CD11b+ Ly6G+), eosinophils (CD3ε − TCRβ− CD19− Ly6G- CD11b+ SiglecF+), alveolar macrophages (CD3ε− TCRβ− CD19− Ly6G- CD64+ F4/80+ SiglecF+ CD11b-), interstitial macrophages (CD3ε− TCRβ− CD19− Ly6G- CD64+ F4/80+ SiglecF- CD11b+) and DCs (CD3ε− TCRβ− CD19− Ly6G− CD64− F4/80− CD11c+ MHCII+).

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