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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

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	ZEN black SP5; MetaMorph V7.8.13.0; BD FACSDiVa; Image Studio Ver 5.2; Gen5.3.03; ImageJ 1.5Oi; FlowJo v10
Data analysis	CellProfiler 3.1.8 for measurement of microtubule intensity and SQSTM1/p62 puncta; MATLAB, GraphPad Prism 7, and Excel are for processing quantification results; SimBiology package in MATLAB is for PK-PD simulation. All data are shown as mean ± s.d. and two-tailed Student's t-tests were used for statistical analysis.

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. 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

The data generated for this study are available from the correspondence authors on reasonable request. Figure 1-4 and extended data figure 1-18 have associated raw data.

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	Sample sizes were determined based on previous experience or similar published studies. Experiments were performed with independent samples or mouse groups. Related reference: Nature 550, 255–259; Cell 178, 1-14.
Data exclusions	No data were excluded.
Replication	For ex vivo, in vivo, and tissue culture experiments, experiments were repeated multiple times. All attempts at replication were successful. There were at least 3 independent experiments for all data shown in this studies
Randomization	The allocation of samples and mice into treatment groups was random.
Blinding	Investigators were blinded when testing anti-inflammatory activity of plasma samples in ex vivo myeloid cell activation assays. At least two investigators were blinded for image quantification. Investigators were blinded to group allocation during data collection and analysis.

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
☐	☒ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used

For western blotting:
GAPDH (Cell Signaling Technology, #2118) https://www.cellsignal.com/products/primary-antibodies/gapdh-14c10-rabbit-mab/2118

Nrf2 (Cell Signaling Technology, #12721)
https://www.cellsignal.com/products/primary-antibodies/nrf2-d1z9c-xp-rabbit-mab/12721

phospho-JNK (Cell Signaling Technology, #9255) https://www.cellsignal.com/products/primary-antibodies/phospho-sapk-jnk-thr183-tyr185-g9-mouse-mab/9255

SQSTM1/p62 (Cell Signaling Technology, #23214) https://www.cellsignal.com/products/primary-antibodies/sqstm1-p62-d6m5x-rabbit-mab-rodent-specific/23214

phospho-S349-SQSTM1/p62 (Cell Signaling Technology, #16177)
https://www.cellsignal.com/products/primary-antibodies/phospho-sqstm1-p62-ser349-e7m1a-rabbit-mab/16177

phospho-Y564-SHP-1 (Cell Signaling Technology, #8849) https://www.cellsignal.com/products/primary-antibodies/phospho-shp-1-tyr564-d11g5-rabbit-mab/8849

LC3B (Cell Signaling Technology, #2775)
https://www.cellsignal.com/products/primary-antibodies/lc3b-antibody/2775

mouse anti-rabbit IgG conformation specific (Cell Signaling Technology, #3678)

IL-1beta (R&D Systems, AF-401)
https://www.rndsystems.com/products/mouse-il-1beta-il-1f2-antibody_af-401-na

GDF15 (Abcam, ab189358 and ab105738)
https://www.abcam.com/gdf15-antibody-6d12h10e4-ab189358.html

home-made anti-mouse GDF15 antibody

tubulin (Millipore Sigma, DM1alpha, T6199)
https://www.sigmaaldrich.com/catalog/product/sigma/t9026?lang=en&region=US&gclid=Cj0KCQiAvP6ABhCjARIsAH37rbT6meB9Uak14IcobfCyJfMRefu8lDrXxxoT9qeieqIvlM223w7onmQaArunEALw_wcB

Keap1 (Millipore Sigma MABS514)
https://www.emdmillipore.com/US/en/product/Anti-Keap1-Antibody-clone-144,MM_NF-MABS514

SHP-1 (Santa Cruz, sc-7289)
https://www.scbt.com/p/sh-ptp1-antibody-d-11

JNK (Santa Cruz, sc-7345)
https://www.scbt.com/p/jnk-antibody-d-2?requestFrom=search

actin (Santa Cruz, sc-47778)
https://www.scbt.com/p/beta-actin-antibody-c4?requestFrom=search

S591-SHP-1 antibody (ECM Biosciences, SP1531)
https://ecmbio.com/products/sp1531

anti-rabbit IgG (Invitrogen, 535571)
anti-mouse IgG (Invitrogen, 35518)
anti-rat IgG (LI-COR, 926-68076)

For immunostaining:
HNF4 (Abcam, ab181604)
https://www.abcam.com/hnf-4-alpha-antibody-epr16885-chip-grade-ab181604.html

F4/80 antibody (Bio-Rad, MCA497GA)
https://www.bio-rad-antibodies.com/monoclonal/mouse-f4-80-antibody-cl-a3-1-mca497.html?f=purified

For FACS analysis:
Ly-6G antibodies (Biolegend, 127614 and 127608)
https://www.biolegend.com/en-us/products/apc-anti-mouse-ly-6g-antibody-6115

GDF15 ELISA (R&D Systems DY-6385)

Validation

All antibodies, except the home-made one against GDF15, the GDF15 monoclonal antibody and the GFRAL monoclonal antibody, were from commercial vendors and validated by the companies, including Cell Signaling, Abcam, Millipore Sigma, Santa Cruz, R&D Systems, ECM Biosciences, Invitrogen, Bio-Rad, and Biolegend. Evaluation information could be accessed on company's website using the product catalog numbers listed above. The evaluation of primary antibodies were performed using samples with either gene depletion or overexpression as mentioned in company websites and all linkers were listed above.

For home-made anti-mouse GDF15 antibodies, we tested it by performing western blotting with liver samples collected from wild-type and GDF15 knockout mice. We also perform overexpression of human and mouse GDF15 in HEK 293T cells to prove the specificity of antibodies.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK 293T cells (ATCC), THP-1 (ATCC), BMDM is a kind gift from Dr. Jonathan Kagan
Authentication	Authentication of HEK 293T and THP-1 was not performed.
Mycoplasma contamination	HEK 293T and THP-1 were mycoplasma-free.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

Animals and other organisms

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

Laboratory animals	Mice at age 8-11 weeks old were used in the study. Male and female wild-type C57BL/6J were bought from Jackson Laboratories. GDF15-/- and GFRAL-/- mice were generated as previously described in reference 47 and 30 respectively.
Wild animals	No wild animals were used.
Field-collected samples	No field-collected samples were used.
Ethics oversight	The animal protocol was approved by the Harvard Medical Area Standing Committee on Animal.

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

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	Murine peritonitis was induced by i.p. injection of either zymosan or MSU, peritoneal exudate cells were collected and stained with the antibody against Ly-6G. Then cells were fixed with 4% PFA. For ex vivo assays, isolated neutrophils were labeld with Ly-6G, treated as mentioned in Metods, and then fixed with PFA.
Instrument	BD LSRII flow cytometry analyzer was used in the study.
Software	Dta collection was with BD FACSDiVa and analyzed with FlowJo v10.
Cell population abundance	For in vivo inflammation assays, Ly-6G+ population abundance is dependent on treatment. For ex vivo assays, population abundance was shown in figure 1.
Gating strategy	To discern single cells, FSC/SSC was used. Samples with or without staining were used to set boundaries between negative and positive cells.

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