nature portfolio

Corresponding author(s): Nicoletta Filigheddu

Last updated by author(s): Feb 24, 2026

Reporting Summary

Nature Portfolio 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 Portfolio policies, see our Editorial Policies 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	Real Time qPCR: StepOnePlus™ (96-well) Real-Time PCR Systems (Thermo Fisher Scientic) RNA quality check: BioAnalyzer 2100 (Agilent) Sequencing for RNAseq: Illumina® NovaSeq 6000 system Chemiluminescent signals detection: ChemiDoc Touch Imaging System Absorbance signal: VICTOR™ X4 2030 Series Multilabel Plate Readers (PerkinElmer) Phase contrast images: Leica DMi1 Inverted Microscope (Leica Biosystem) Micro-LC Eksigent Technologies system interfaced with a 5600+ TripleTOF system (SCIEX) UHPLC Vanquish system (Thermo Fisher Scientific) coupled with an Orbitrap Q-Exactive Plus (Thermo Fisher Scientific). UHPLC Vanquish system (Thermo Scientific) coupled to a Q-Exactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer Q-Exactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer (Thermo Scientific) Fluorescence Imaging: : EVOS XL Core Imaging System (Thermo Fisher Scientific) Confocal microscopy: Leica SP8 (Leica Biosystem) Oxygen consumption analysis: OROBOROS Oxygraph-2k (Oroboros Instruments) Mouse grip strenght meter: BIO-GS4 (Bioseb) TreadMill test: LE8710M (Panlab Harvard Apparatus) Blood glucose concentration: ONETOUCH Verio Reflect blood glucometer (Lifascan) Indirect calorimetry: Oxylet LE 1305 Physiocage (Panlab Harvard Apparatus)
Data analysis	Graphpad Prism version 10.4.0 JMicroVision 1.2.7 ImageLab Biorad

MicrosoftExcel 365
ImageJ FIJI 1.54p
Mouse reference genome: Mouse GRCm38/mm10
High-resolution respirometry analysis: DatLab 7.4
Respiratory quotient and energy expenditure analysis: Metabolism v3.0.01
Protein Pilot software v. 4.2 (SCIEX)
Mascot v. 2.4 (Matrix Science Inc.)
PeakView 2.2 (SCIEX)
MarkerView 1.2 (SCIEX)
MaxQuant software (version 1.6.14)
MetaboAnalyst software (https://www.metaboanalyst.ca/)
Thermo Xcalibur software (version 4.1.31.9, Thermo Fisher Scientific)

Sequence alignment for RNAseq: STAR aligner
RNAseq reads were assigned to the corresponding genes using featureCounts
RNAseq annotation: Gencode (vM22)
RNAseq differential gene expression analysis:DESeq2 R package
Gene Set Enrichment Analysis: Ingenuity Pathway (Qiagen)

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

Proteomic data are available via ProteomeXchange with the identifier PXD042024 [https://www.ebi.ac.uk/pride/archive/projects/PXD042024].
The RNA-Seq data are available in the NCBI GEO with the ID GSE231768 [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE231768].

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	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used.* *Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected.* *Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status).* *Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.)* *Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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	Sample sizes for experiments involving VDBP injection in Gc KO mice were selected to ensure adequate statistical power while minimizing variability and animal use. Assuming a type I error of 0.05, a power of 80%, a mean tibial anterior weight in Gc KO mice of 51.39 mg and a corresponding standard deviation of 3.61 (preliminary data), 8 mice per group were needed to observe a mean difference of at least 10% of tibial anterior weight between VDBP injected and not-injected Gc KO mice. For cachexia experiments, sample size was determined based on previous studies using comparable Lewis lung carcinoma–induced cachexia models: Camperi et al., 2017, Oncotarget (doi:10.18632/oncotarget.15583). Zhang, G. et al., 2027, Nat Commun (doi.org/10.1038/s41467-017-00726-x)
Data exclusions	Outliers were identified using the interquartile range (IQR) method and excluded from the analysis. For Oroboros analysis, values were excluded a priori from statistical analysis when technical anomalies occurred during data acquisition.
Replication	For each in vitro experiment, data derive from independent analyses performed on different days and with cells at different passages. Experiments involving animals, with the indicated sample size, were performed simultaneously to minimize variability.
Randomization	Mice were randomly assigned to the experimental groups. For in vitro experiments, cells were cultured under identical conditions (cell number and medium) prior to treatment.
Blinding	Investigators were blinded to experimental groups whenever possible. In cachexia experiments, blinding was not always possible for tumor-bearing mice due to the recognizable phenotype. However, investigators quantifying experimental outcomes were blinded to group allocation. The investigators quantifying the experimental outcomes were blind to the treatments, and the statistic evaluation of the experimental data was performed by another investigator not directly involved in data collection and parameter measurement (L.S.).

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

Primary antibodies:
Anti-β-actin (AC-15; mouse monoclonal; Sigma-Aldrich, #A5441);
Anti-DRP1 (8/DLP1; mouse monoclonal; BD Biosciences, #611113);
Anti-laminin (rabbit polyclonal; Dako, #Z0097);
Anti-LC3B (rabbit polyclonal; Proteintech, #18725-1-AP);
Anti-LC3B (mouse polyclonal; Nanotools, #AB_2943418);
Anti-LRP2 (rabbit, polyclonal; Proteintech, #19700-1-AP);
Anti-MyHC sarcomere (MF-20; mouse monoclonal; Developmental Studies Hybridoma Bank);
Anti-MyHC type IIa (SC-71; mouse monoclonal; Developmental Studies Hybridoma Bank);
Anti-MyHC type IIb (BF-F3; mouse monoclonal; Developmental Studies Hybridoma Bank);
Anti-neurofilament (chicken polyclonal; Abcam, #ab4680);
Anti-TOM20 (rabbit monoclonal; Proteintech);
Anti-tubulin (mouse monoclonal; Santa Cruz Biotechnology, #sc-32293);
Anti-VDAC (rabbit polyclonal; Cell Signaling Technology, #4661);

Anti-VDBP (rabbit polyclonal; Proteintech, #16922-1-AP).

Secondary antibodies:
Anti-chicken IgY (H+L) Alexa Fluor 546 (goat; Thermo Fisher Scientific, #A11040);
Anti-mouse IgG (H+L) Alexa Fluor 488 (donkey; Thermo Fisher Scientific, #A21202);
Anti-mouse IgG (H+L) Alexa Fluor 546 (goat; Thermo Fisher Scientific, #A11003);
Anti-mouse IgG HRP-labelled (goat; PerkinElmer, #NEF822001EA);
Anti-mouse IgG1 Alexa Fluor 488 (goat; Thermo Fisher Scientific, #A21121);
Anti-mouse IgM Alexa Fluor 546 (goat; Thermo Fisher Scientific, #A21045);
Anti-rabbit IgG (H+L) Alexa Fluor 405 (goat; Thermo Fisher Scientific, #A31556);
Anti-rabbit IgG (H+L) Alexa Fluor 488 (donkey; Thermo Fisher Scientific, #A21206);
Anti-rabbit IgG HRP-labelled (goat; PerkinElmer, #NEF812001EA).

Validation

Primary antibodies:

β-actin (AC-15) – Sigma-Aldrich (#A5441). This antibody can be found in 12,753 citations. The manufacturer provides antibody testing and validation data:
https://www.sigmaaldrich.com/IT/en/product/sigma/a5441

DRP1 (8/DLP1) – BD Biosciences (#611113). This antibody can be found in 145 citations. The manufacturer provides antibody testing and validation data:
https://www.bdbiosciences.com/en-pt/products/reagents/microscopy-imaging-reagents/immunofluorescence-reagents/purified-mouse-anti-dlp1.611113

Laminin – Dako (#Z0097). This antibody can be found in 191 citations. The manufacturer provides antibody testing and validation data:
https://www.citeab.com/antibodies/3382922-z0097-laminin

LC3B – Proteintech (#18725-1-AP). This antibody can be found in 387 citations. The manufacturer provides antibody testing and validation data:
https://www.ptglab.com/products/MAP1LC3B-Specific-Antibody-18725-1-AP.htm

LC3B – Nanotools (#AB_2943418). This antibody can be found in 183 citations. The manufacturer provides antibody testing and validation data: https://www.nanotools.de/en/shop/artikel/AB_L-0260-100_LC3-2G6.php

LRP2 – Proteintech (#19700-1-AP). This antibody can be found in 19 citations. The manufacturer provides antibody testing and validation data: https://www.ptglab.com/products/LRP2-Specific-Antibody-19700-1-AP.htm?srsltid=AfmBOooz3hOtusoqQghcpe13sg0H0E9CuAd1Lw8c_078RdC9B2Aguuyo
Antibody specificity was further validated in this study by siRNA-mediated knockdown of LRP2 and assessment of protein expression by immunofluorescence.

MyHC sarcomere (MF-20) – Developmental Studies Hybridoma Bank. This antibody can be found in 2,631 citations. The manufacturer provides antibody testing and validation data:
https://dshb.biology.uiowa.edu/MF-20

MyHC type IIa (SC-71) – Developmental Studies Hybridoma Bank. This antibody can be found in 969 citations. The manufacturer provides antibody testing and validation data:
https://dshb.biology.uiowa.edu/SC-71

MyHC type IIb (BF-F3) – Developmental Studies Hybridoma Bank. This antibody can be found in 709 citations. The manufacturer provides antibody testing and validation data: https://dshb.biology.uiowa.edu/BF-F3

Neurofilament – Abcam (#ab4680). This antibody can be found in 191 citations. The manufacturer provides antibody testing and validation data:
https://www.abcam.com/en-us/products/primary-antibodies/neurofilament-heavy-polypeptide-antibody-ab4680

TOM20 – Proteintech (#11802-1-AP). This antibody can be found in 760 citations. The manufacturer provides antibody testing and validation data: https://www.ptglab.com/products/TOM20-Antibody-11802-1-AP.htm

Tubulin – Santa Cruz Biotechnology (#sc-32293). This antibody can be found in 672 citations. The manufacturer provides antibody testing and validation data:https://www.scbt.com/it/p/alpha-tubulin-antibody-dm1a

VDAC – Cell Signaling Technology (#4661; D73D12). This antibody can be found in 422 citations. The manufacturer provides antibody testing and validation data: https://www.cellsignal.com/products/primary-antibodies/vdac-d73d12-rabbit-monoclonal-antibody/4661

Vinculin – Proteintech (#66305-2-Ig; 3A11F8). This antibody can be found in 2 citations. The manufacturer provides antibody testing and validation data: https://www.ptglab.com/products/Vinculin-Antibody-66305-2-Ig.htm

VDBP – Proteintech (#16922-1-AP). This antibody can be found in 12 citations. The manufacturer provides antibody testing and validation data:https://www.ptglab.com/products/VDBP,GC-Antibody-16922-1-AP.htm
Antibody specificity was further validated in this study using VDBP-null ($Gc^{-/-}$) mice.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	C2C12 murine myoblasts were purchased from the European Collection of Authenticated Cell Cultures (catalog number: 91031101, ECACC). Human primary myoblasts were purchased from William Cook Europe ApS (catalog number: P01062-17M; derived from a 17-year-old male subject). Lewis lung carcinoma (LLC) cells were kindly provided by Prof. Paola Costelli (University of Torino) (catalog number: CRL-1642, ATCC).
Authentication	The cell lines used in the study were not authenticated.
Mycoplasma contamination	The cell lines used in the study were periodically tested for mycoplasma contamination. Only mycoplasma-free cells were used.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this 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	Male C57BL/6J wild-type mice were purchased from Charles River Laboratories. Vitamin D–binding protein–null ($Gc^{-/-}$) mice, with a systemic lack of VDBP, were kindly provided by Richard Kew (Stony Brook University, New York). Mice were housed under standard conditions with ad libitum access to food and water. Animal experiments are reported in accordance with the ARRIVE guidelines. All procedures were approved by the Institutional Animal Care and Use Committee at the University of Piemonte Orientale and were authorized after ministerial clearance (Italian Ministero della Salute, Authorization n. DB064.25).
Wild animals	No wild animals were used in the study.
Reporting on sex	In vivo experiments were conducted in male mice only to maintain consistency with previous studies in the Gc KO model and to minimize additional biological variables in this proof-of-concept work, enabling direct comparison with the existing literature. Future studies will be important to assess potential sex-dependent differences.
Field-collected samples	No field-collected samples were used in this study.
Ethics oversight	Animal experiments were performed according to procedures approved by the Institutional Animal Care and Use Committee at the University of Piemonte Orientale and Italian Ministero della Salute (Protocol n. DB064.25).

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

Plants

Seed stocks	No plants were used in the study
Novel plant genotypes	No plants were used in the study
Authentication	No plants were used in the study