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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	The software used for data collection in this study include Bio-Rad CFX Manger 3.1 (version 3.1.1517.0823), CytExpert (version2.4.0.28), Dragonfly (version 2022.1.0.1259), EthoVision XT (version 15.0.1418), Image Lab (version 5.1), LAS (version 4.12.0.86), LAS X (version 3.3.0.16799), NIS-Elements (version 4.50.00), NRecon Reconstruction Software (version 1.7.4.2), cellSens Dimension 2.3 (Build 18987), SKyScan 1272 (version 1.2.0), Wave Controller Software (version 2.6.1), and ZEN 2009 Light Edition. All software are commercially or freely available.
Data analysis	The software used for data analysis in this study include EdgeR (version 3.32.0), GraphPad Prism (version 7.00), HISAT (version 2.0), ImageJ (version 2.1.0), SOHA (version 3.4.0.0), and StringTie (version 1.3.0).

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

All data are presented in the main text or Supplementary Materials. RNA-seq data have been deposited in the Gene Expression Omnibus (GEO) under accession number GSE198848. Gene information of C. elegans hrg-9 (R186.1) and hrg-10 (Y80D3A.9) are available in Wormbase (https://wormbase.org). Information of other

HRG-9/TANGO2 family genes (NM_152906.7, NM_138583.2, NM_001003781.1, and NM_001181256.1) are available in NCBI (https://www.ncbi.nlm.nih.gov). Source data are provided with this paper.

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 chosen based on prior studies with similar experimental paradigms: n = 3 for gene expression experiments (Ref. 10,11), C. elegans experiments (except ZnMP experiments, Ref. 10,11,13), mammalian cell experiments (Ref. 35,44), and yeast haem sensor experiments (Ref. 19); n = 10-30 zebrafish larvae for heartbeat quantification (Ref. 46); n = 30-40 worms for ZnMP quantification (Ref. 12,13). No statistical method was used to predetermine sample size.
Data exclusions	No data were excluded from the analyses.
Replication	All quantitative experiments (except Extended Data Fig. 3a, which was done in duplicate) were performed in three biological replicates in independent experiments. All attempts at replication were successful.
Randomization	For C. elegans haem treatment experiments and RNAi experiments, the synchronized worms were randomly allocated to different treatment conditions. For ZnMP staining experiments, the stained worms were randomly picked from each treatment for imaging. For zebrafish experiments, zebrafish larvae of each treatment group were randomly picked for analysis. Samples were assessed in random order.
Blinding	For RNA-seq analysis, researchers were blinded to experimental conditions. Blinding was not applied to other experiments because each of these experiments was performed by a single researcher and the genotypes of the cells, yeast, and zebrafish had to be identified according to the experimental designs.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	Ctt1p (generated by Amit Reddi's lab, Dilution 1:1000) GAPDH (Genetex, CAT GTX100118, Dilution 1:1000 for western on yeast cells) GAPDH (Santa Cruz, CAT sc-32233, Dilution 1:5000 for western on human cells) FLAG (Sigma-Aldrich, CAT F1804, Dilution 1:1000) COX IV (Abcam, CAT ab16056, Dilution 1:1000) TANGO2 (Proteintech, CAT 27846-1-AP, Dilution 1:600) β-Actin (Huabio, CAT R1207-1, Dilution 1:5000) HRP-conjugated goat-anti-rabbit IgG (Jackson ImmunoResearch, 111-035-003, Dilution 1:5000) HRP-conjugated goat-anti-mouse IgG (Jackson ImmunoResearch, 115-035-003, Dilution 1:5000) Alexa Fluor 568-conjugated goat-anti-rabbit IgG (Life technologies, A-11036, Dilution 1:5000) Alexa Fluor 488-conjugated goat-anti-mouse IgG (Life technologies, A-11029, Dilution 1:5000)
Validation	Ctt1p: yeast, western, validated by (J Biol Chem 2018, 293:12378-12393) GAPDH: yeast, western, validated on manufacture's website: https://www.genetex.com/Product/Detail/GAPDH-antibody/GTX100118 GAPDH: human, western, validated on manufacture's website: https://www.scbt.com/p/gapdh-antibody-6c5/

FLAG: human, immunofluorescence, validated on manufacture's website: https://www.sigmaaldrich.com/US/en/product/sigma/f1804
COX IV: human, western, immunofluorescence, validated on manufacture's website: https://www.abcam.com/cox-iv-antibody-mitochondrial-loading-control-ab16056.html
TANGO2: human, mouse, western, validated on manufacture's website: https://www.ptglab.com/products/C22orf25-Antibody-27846-1-AP.htm
β-Actin: mouse, western, validated on manufacture's website: https://www.huabio.com/products/beta-actin-antibody-polyclonal-r1207-1
HRP-conjugated goat-anti-rabbit IgG: western, validated on manufacture's website: https://www.jacksonimmuno.com/catalog/products/111-035-003
HRP-conjugated goat-anti-mouse IgG: western, validated on manufacture's website: https://www.jacksonimmuno.com/catalog/products/115-035-003
Alexa Fluor 568-conjugated goat-anti-rabbit IgG: immunofluorescence, validated on manufacture's website: https://www.thermofisher.com/antibody/product/Goat-anti-Rabbit-IgG-H-L-Highly-Cross-Adsorbed-Secondary-Antibody-Polyclonal/A-11036
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Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293 cell was obtained from ATCC. MEL (clone DS19) was a gift from Dr. Barry Paw's lab. This cell line is also available at Creative Bioarray.
Authentication	Cells were evaluated based on morphological inspection.
Mycoplasma contamination	Cells were routinely tested for mycoplasma (once every 2-3 months). None of the cell lines used in this study was contaminated with mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

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

Laboratory animals	Caenorhabditis elegans strains used in this study include the N2 Bristol strain, IQ6011 (hrg-1p::gfp), RT130 (VIT-2::GFP), and MGH41 (PGP-2::GFP). Mutant worms and the other transgenic worms used in this study were generated in the N2 background. The worms were used at the ages of 0 day (newly hatched) and 3-4 days (adult). This study used three zebrafish (Danio rerio) strains, the wild type AB strain, Tg(globin-LCR:eGFP) transgenic strain, and tango2-knockout strain. The tango2-knockout fish was generated in our lab. Adult males and females between 3 and 6 months of age were mated to produce eggs, and the progeny were analyzed for phenotypes.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The protocols for zebrafish experiments were approved by the Institutional Animal Ethics Committee of Zhejiang University.

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	1) HEK293 cells and MEL cells were stained with 200 nM tetramethylrhodamine, ethyl ester (TMRE) for 20 min. The stained cells were washed twice with 1xPBS prior to sorting. 2) Single-cell suspensions were prepared from the Tg(globin-LCR:eGFP) transgenic zebrafish embryos. The cells were filtered through 70 μm and 40 μm cell strainers prior to sorting.
Instrument	CytoFLEX LX Flow Cytometer (Beckman)
Software	CytExpert (version 2.4.0.28)

Cell population abundance	1) Mammalian cell experiment: 10,000 cells were analyzed for each sample and almost all cells (>99%) cells were positive for TMRE. 2) Fish experiment: 50,000 cells were analyzed for each sample and ~5% cells were positive for GFP.
Gating strategy	The forward versus side scatter (FSC vs SSC) gating was used to identify cells from cell aggregates.

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