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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	1. Q-PCR: Bio-Rad CFX Manager, version 3.1.1517.823 2. C. elegans images: ZEN 2012 (Blue edition), version 1.1.13346.204 3. Cell images: LSM 710 Zeiss Confocal Microscope Control software 4. TCGA datasets for lung cancer: cBioPortal (www.cbioportal.org), version 3.3.2 5. Microscale thermophoresis (MST) assay: MO.Control, version 2.3.0.7385 6. Circular dichroism (CD) assay: Bio-Kine 32, version 4.74 7. Patient prognosis: Kaplan-Meier-Plotter (www.kmplot.com), version 2017.10.07 8. C. elegans codon adapter (https://worm.mpi-cbg.de/codons/cgi-bin/optimize.py), no version information
Data analysis	1. Colony (soft-agar) counting and immunoblot quantification: Image J, version 1.47 2. Sequence alignment display: Jalview, version 18.0.0.0 3. SAR1B structure display: PyMOL, version 2.2.3 4. Display of columns, dots, boxes and curves: Graphpad Prism, version 8.2.1 5. Dissociation constant (Kd) calculation: Graphpad Prism, version 8.2.1 6. IC50 calculation: Graphpad Prism, version 8.2.1 7. Statistical analysis: Graphpad Prism, version 8.2.1 8. Colocalization analysis: Image J, version 1.53c 9. Murine gene tissue distribution analysis: Pheatmap package in R version 4.0.3

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 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 authors declare that all data supporting the findings of this study are available within the paper. Uncropped gel blots are shown in Supplementary Figure 1. Raw data for all animal-related experiments in main and extended figures (Fig. 3, Fig. 4, Extended Data Fig. 9, Extended Data Fig. 11 and Extended Data Fig. 12) are provided as source data. Publicly available datasets generated by others used in this study are as following:
Database of lung cancers: www.cbioportal.org
Gene expression database of murine tissues: www.informatics.jax.org
Database of lung cancer patient prognosis: www.kmplot.com

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 method was used to predetermine sample size. The mouse sample size in our experiments were determined according to similar analysis in the literature (Toshiro Moroishi et al., 2016, Cell.). Worm sample size were also determined according to similar analysis in the literature (Sakiko Honjoh et al., 2009, Nature).
Data exclusions	1. For lifespan assays, worms that crawled off the plate or underwent vulva blasting could cause irregular death and were not included in the data. This exclusion criteria has been established and extensively used in the field. 2. For subcutaneous xenograft tumor growth assay, mice with evidently ulcerated tumors before the last day were euthanized and the corresponding tumor data were not included. This exclusion criteria has been established by IACUC at Pony Testing International Group where we conducted our study. 3. For lung orthotopic xenograft tumors, mice with cells incorrectly injected into thoracic cavities, instead of transplanted into left lung lobes, were excluded.
Replication	All experiments were repeated for at least three times and reached similar results.
Randomization	For all experiments, samples/worms/mice were randomly allocated into groups.
Blinding	Investigators were blinded to group allocation of worms and mice during data collection and analysis. For other experiments, each experiment was repeated by different investigators and reached similar results

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

Antibodies used in this study were: anti-Flag (Sigma, F7425; 1:10,000 dilution in immunoblotting), anti-HA (CST, 3724; 1:10,000 dilution in immunoblotting), anti-GFP (Abcam, 290; 1:10,000 dilution in immunoblotting), anti-p-S6K1 (CST, 9234; 1:1,000 dilution in immunoblotting), anti-S6K1 (CST, 9202; 1:1,000 dilution in immunoblotting), anti-mTOR (CST, 2983; 1:100 dilution in immunostaining), anti-LAMP2 (Abcam, 25631; 1:100 dilution in immunostaining), anti-SAR1A (Proteintech, 22291-1-AP; 1:1,000 dilution in immunoblotting), anti-SAR1B (Proteintech, 22292-1-AP; 1:1,000 dilution in immunoblotting; 1:50 dilution in immunoprecipitation), anti-GAPDH (Abcam, 128915; 1:10,000 dilution in immunoblotting), anti-NPRL2 (Sigma, SAB1305758; 1:1,000 dilution in immunoblotting), anti-NPRL3 (Sigma, HPA011741; 1:1,000 dilution in immunoblotting), anti-DEPDC5 (Sigma, SAB1302644; 1:500 dilution in immunoblotting), anti-Sec13 (Santa Cruz, 514308; 1:1,000 dilution in immunoblotting), anti-Mios (CST, 13557; 1:1,000 dilution in immunoblotting), anti-WDR24 (Proteintech, 20778-1-AP; 1:1,000 dilution in immunoblotting; 1:50 dilution in immunoprecipitation), anti-WDR59 (CST, 53385; 1:1,000 dilution in immunoblotting), anti-Sestrin2 (Proteintech, 10795-1-AP; 1:5,000 dilution in immunoblotting), anti-Sestrin1 (Proteintech, 21668-1-AP; 1:1,000 dilution in immunoblotting), anti-Sestrin3 (Abgent, AP12471c; 1:1,000 dilution in immunoblotting), anti-MYL1 (Proteintech, 15814-1-AP; 1:1,000 dilution in immunoblotting), anti-CKM (Proteintech, 18712-1-AP; 1:1,000 dilution in immunoblotting), anti-MYOD1 (Proteintech, 18943-1-AP; 1:1,000 dilution in immunoblotting), anti-α-Tubulin (CST, 2144; 1:10,000 dilution in immunoblotting), anti-β-Actin (Sigma, A5441; 1:10,000 dilution in immunoblotting), anti-p-S6 (CST, 4858; 1:100 dilution in immunohistochemistry), anti-LC3B (Novus Biologicals, NB100-2220; 1:100 dilution in immunostaining and immunohistochemistry), anti-Ki-67 (Abcam, 16667; 1:100 dilution in immunohistochemistry), anti-rabbit secondary antibody Alexa fluor 488 (Thermo, A21206; 1:100 dilution) and anti-mouse secondary antibody Alexa fluor 555 (Thermo, A31570; 1:100 dilution).

Validation

1. Rabbit anti-Flag pAb (Sigma F7425): Validated by the supplier with following notes (1) Species reactivity: all. (2) Application: The antibody recognizes the FLAG epitope located on FLAG-tagged fusion proteins, applying dot blot, WB, IP and ICC assays.
2. Rabbit anti-HA mAb (CST 3724): Validated by the supplier with following notes (1) Species reactivity: all. (2) Application: HA-Tag (C29F4) Rabbit mAb detects exogenously expressed proteins containing the HA epitope tag. Western Blotting 1:1000, Immunoprecipitation 1:50, Immunohistochemistry (Paraffin) 1:800 - 1:3200, Immunofluorescence (Immunocytochemistry) 1:800 - 1:1600, Flow Cytometry 1:800 - 1:1600, Chromatin IP 1:50.
3. Rabbit anti-GFP pAb (Abcam 290): Validated by the supplier with following notes (1) Species reactivity: all. (2) This antibody recognizes GFP, EGFP, and venus YFP. (3) Application: ELISA, ICC, IHC, IP and WB.
4. Rabbit anti-p-S6K1 (CST 9234): Validated by the supplier with following notes (1) Species Reactivity: Human, Mouse, Rat, Monkey. (2) Application: Western Blotting. Also validated in the literature (Yasemin Sancak et al., 2008, Science).
5. Rabbit anti-S6K1 (CST 9202): Validated by the supplier with following notes (1) Application: Western Blotting 1:1000, Immunoprecipitation 1:50. (2) Human, Mouse, Rat, Monkey. Also validated in the literature (Yasemin Sancak et al., 2008, Science).
6. Rabbit anti-mTOR (CST 2983) mAb and mouse anti-LAMP2 (Abcam 25631) mAb: Validated in this study by immunostaining in Extended Data Fig. 1i, Extended Data Fig. 2c and Extended Data Fig. 4c.
7. Rabbit anti-SAR1A pAb (Proteintech 22291-1-AP): Validated by the supplier with following notes (1) Reactivity: Human, Mouse, Rat. (2) Applications: WB, IHC,ELISA. Also validated in this study: Extended Data Fig. 1o.
8. Rabbit anti-SAR1B pAb (Proteintech 22292-1-AP): Validated by the supplier with following notes (1) Reactivity: Human, Mouse, Rat. (2) Applications: WB, IHC,ELISA. Also validated in this study: Extended Data Fig. 1o.
9. Rabbit anti-Mios (CST 13557) mAb: Validated by the supplier with following notes (1) Reactivity: Human, Mouse, Rat. (2) Applications: WB, IP. Also validated in this study: Extended Data Fig. 3i.
10. Rabbit anti-GAPDH mAb (Abcam 128915): Validated by the supplier with following notes (1) Species reactivity: Human, African green monkey. (2) Application: WB, IP, Flow Cyt, ICC/IF, IHC-P.
11. Rabbit anti-NPRL2 pAb (Sigma SAB1305758): Validated by the supplier with following notes (1) Species reactivity: human. (2) Application: western blot: 1:1000.
12. Rabbit anti-NPRL3 pAb (Sigma HPA011741): Validated by the supplier with following notes (1) Species reactivity: human. (2) Application: immunofluorescence: 0.25-2 µg/mL, immunohistochemistry: 1:50-1:200.
13. Rabbit anti-DEPDC5 pAb (Sigma SAB1302644): Validated by the supplier with following notes (1) Species reactivity: human. (2) Application: western blot: 1:1000.
14. Mouse anti-Sec13 mAb (Santa Cruz 514308): Validated by the supplier with following notes (1) Species reactivity: mouse, rat and human. (2) Application: WB, IP, IF and ELISA.
15. Rabbit anti-WDR24 pAb (Proteintech 20778-1-AP): Validated by the supplier with following notes (1) Species reactivity: human, mouse, rat. (2) Application: WB, IP, IHC, IF, ELISA.
16. Rabbit anti-WDR59 mAb (CST 53385): Validated by the supplier with following notes (1) Species reactivity: Human, Monkey. (2) Application: WB 1:1000, IP 1:50.
17. Rabbit anti-Sestrin1 pAb (Proteintech 21668-1-AP): Validated in a previously published paper (Dandan Xu et al., 2019, Am J Physiol Endocrinol Metab.).
18. Rabbit anti-Sestrin2 pAb (Proteintech 10795-1-AP): Validated by the supplier with following notes (1) Tested species reactivity: Human, Mouse, Rat. (2) Application: WB, IF, IHC and IP.
19. Rabbit anti-Sestrin3 pAb (Abgent AP12471c): Validated in a previously published paper (Dandan Xu et al., 2019, Am J Physiol Endocrinol Metab.).
20. Rabbit anti-MYL1 pAb, Rabbit anti-CKM pAb and Rabbit anti-MYOD1 pAb were validated in this study by immunoblotting in Extended Data Fig. 8c.
21. Rabbit anti-α-Tubulin pAb (CST 2144): Validated by the supplier with following notes (1) Species reactivity: Human, Mouse, Rat, Monkey, D. melanogaster, Bovine. (2) Application: WB 1:1000, IHC 1:50, IF1:25, Flow Cytometry 1:50.
22. Mouse anti-β-Actin mAb (Sigma A5441): Validated by the supplier with following notes (1) Species reactivity: pig, Hirudo medicinalis, bovine, rat, canine, feline, human, rabbit, carp, mouse, guinea pig, chicken, sheep. (2) Application: IHC, ELISA, IF: 1:1,000-1:2,000, WB: 1:5,000-1:10,000.
23. Rabbit anti-p-S6 mAb (CST 4858): Validated by the supplier with following notes (1) Application: WB 1:2000, IHC 1:400, IF 1:100, Flow Cytometry 1:25. (2) Species Reactivity: Human, Mouse, Rat, Monkey, Mink, S. cerevisiae.
24. Rabbit anti-LC3B pAb (Novus Biologicals NB100-2220): Validated by the supplier with following notes (1) Species reactivity: Hu, Mu, Rt, Po, Av, Ba, Bv, Ca, Ch, Gp, Ha, In, Pm, Pm, Rb, SyHa, Ze. (2) Application: WB, ELISA, Flow, IB, IF, IHC, IP, ChIP.
25. Rabbit anti-Ki-67 mAb (Abcam 16667): Validated by the supplier with following notes (1) Species reactivity: Mouse, Rat, Human, Common marmoset. (2) Application: Flow Cyt: 1/1000, IHC: 1/200, WB, ICC: 1/250.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T (ATCC CRL-3216), HFL1 (ATCC CCL-153), IMR-90 (ATCC CCL-186), NCI-H650 (ATCC CRL-5835), NCI-H1581 (ATCC CRL-5878), C2C12 (ATCC CRL-1772) and 3T3-L1 (ATCC CL-173).
Authentication	All cell lines were authenticated by STR analysis before use in this study.
Mycoplasma contamination	All cell lines were validated to be free of mycoplasma contamination before use in this study.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

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

Laboratory animals	C. elegans strains (wild-type: N2; MAH240: hlh-30p::hlh-30::gfp; VC2792: sar-1(ok3513) IV/nT1 [qIs51]) were provided by the Caenorhabditis Genetics Center (CGC). Synchronized L1 stage hermaphrodites were used. 8-week-old female BALB/c nude mice and NU/NU Nude mice were purchased from Charles River Laboratories and kept in a specific pathogen-free facility. Mice were kept under ~20 °C with ~50% humidity in a 14-hour light/10-hour dark cycle.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from field.
Ethics oversight	Subcutaneous xenograft tumor experiments were conducted at Pony Testing International Group and followed the guidelines of institutional IACUC. Orthotopic xenograft tumor experiments were performed at Peking University and followed the rules of institutional IACUC.

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