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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	NIS-Elements BR 5.11.01 software was used for immunofluorescence and immunohistochemistry data collection. StepOne Software v2.3 was used for real-time PCR data collection. Gen5 3.04 software was used for absorbance and luminescence data collection. Spectra Manager Ver.2 was used to collect Circular dichroism (CD) data.
Data analysis	Microsoft Excel for Mac Version 16.43 (20110804) was used for Student's t-test (two-tailed, unpaired) analysis. GraphPad Prism 6 for Windows Version 6.01 software was used for Two-way ANOVA test, Spearman correlation and Mantel-Cox test analysis. STAR/2.5.2a was used for sequence alignment; DEseq2/1.26.0 in R3.6.1 was used for RNAseq differential gene analysis. The PMEMD program implemented in AMBER18 molecular dynamics suite was used for simulation analyses, CPPTRAJ was used to calculate the root-mean-square deviation (RMSD) value. Western blots signals were quantified by ImageJ 1.52a.

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

The RNA sequencing dataset is available in Gene Expression Omnibus (GEO) with the accession number GSE163156. The lung squamous cell carcinoma (LUSC) RNAseq datasets were downloaded from the Cancer Genome Atlas (TCGA) data portal (https://portal.gdc.cancer.gov/).The protein structure information (PDB: 1ZW8) is downloaded from protein data bank (https://www.rcsb.org/structure/1zw8). Source data are provided with this paper. All other data supporting the findings of this study are available from the corresponding author on reasonable request.

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. Sample size was determined based on our previous studies and common practice in the field.
Data exclusions	No samples or animals were excluded for the analyses in this study
Replication	Each experiment was repeated twice or more with similar results, unless otherwise noted.
Randomization	As for the mouse experiments, we assigned the animals randomly to different groups.
Blinding	A laboratory technician was blinded to the group allocation and tissue collections during the animal experiments as well as the data analyses. As for other experiments, data collection and analysis were performed blindly.

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

Sigma-Aldrich:
anti-alpha-tubulin (T6199-200UL, WB: 1:5000 dilution),
anti-beta-actin (A2228, WB: 1:3000 dilution),
anti-Flag (M2) (F3165-5MG, WB: 1:5000 dilution, IF: 1:5000 dilution)

Santa Cruz Biotechnology:
anti-Myc (sc-40, WB: 1:500 dilution),
anti-p300 (sc-585, WB: 1:500 dilution),

anti-YAP antibody (sc-101199, IF: 1:200 dilution)

BioLegend:
anti-hemagglutinin (HA) antibody (901503, WB: 1:3000 dilution)

Cell Signaling Technology:
anti-pan TEAD (13295S, WB: 1:1000 dilution),
anti-phospho-YAP (Ser127) (4911S, WB: 1:1000 dilution),
anti-YAP/TAZ (8418S, WB: 1:2000 dilution),
anti-phospho-LATS1 (Ser909) (9157S, WB: 1:1000 dilution),
anti-phospho-LATS1 (Thr1079) (8654S, WB: 1:1000 dilution),
anti-LATS1 (3477S, WB: 1:1000 dilution, IP: 1:300 dilution),
anti-phospho-MST (Thr180/Thr183) (3681S, WB: 1:1000 dilution),
anti-MST1 (3682S, WB: 1:1000 dilution, IP: 1:300 dilution),
anti-phospho-MOB1 (Thr35) (8699S, WB: 1:1000 dilution),
anti-MOB1 (3863S, 1:2000 dilution),
anti-NF2 (12896S, WB: 1:2000 dilution),
anti-KIBRA (8774S, 1:1000 dilution),
anti-SP1 (9389S, WB: 1:1000 dilution),
anti-CBP (7389S, WB: 1:1000 dilution),
and anti-C/EBPalpha (8178T, WB: 1:1000 dilution),
anti-cleaved caspase-3 (9579S, IHC: 1:15 dilution),
anti-YAP (14074S, IHC: 1:20 dilution)

Novus Biologicals:
anti-MTF1 antibody (NBP1-86380, WB: 1:2000 dilution, 1:200 dilution),
anti-MT1A antibody (NBP1-97493, IHC: 1:20 dilution)

Abcam:
anti-Thiophosphate ester antibody (ab92670, WB: 1:1000 dilution),
anti-MTF1 antibody (ab236401, IHC: 1:20 dilution)

Bethyl Laboratories:
anti-MAP4K4/HGK antibody (A301-502A-M, WB: 1:2000 dilution, IP: 1:300 dilution)

Kinexus:
anti-phospho-MAP4K2 (Ser170) antibody (AB-PK646, WB: 1:1000 dilution)

Homemade:
anti-phospho-MTF1 (Ser152) antibody (WB: 1:500 dilution, IHC: 1:20 dilution),
anti-MBP (WB: 1:5000 dilution),
anti-GST (WB: 1:5000 dilution),
anti-YAP (WB: 1:500 dilution),
anti-AMOTL2 (WB: 1:500 dilution)

Validation

Most of the antibodies were validated in-house using knockout/knockdown cells by Western blot and/or immunofluorescence assays to evaluate their appropriate molecular weight bands or correct cellular localization, respectively. Phospho-antibodies were verified using corresponding site mutation constructs and/or displaying the correct expression pattern between different treatments (e.g., kinase activating- or inactivating- stimuli, kinase KO cells, kinase inhibitors).

For the commercial antibodies, anti-pan TEAD (13295S), anti-phospho-YAP (Ser127) (4911S), anti-YAP/TAZ (8418S), anti-phospho-LATS1 (Ser909) (9157S), anti-phospho-LATS1 (Thr1079) (8654S), anti-LATS1 (3477S), anti-phospho-MST (Thr180/Thr183) (3681S), anti-MST1 (3682S), anti-phospho-MOB1 (Thr35) (8699S), anti-MOB1 (3863S), anti-NF2 (12896S), anti-KIBRA (8774S), anti-beta-tubulin (T6199-200UL), anti-alpha-actin (A2228), anti-Flag (M2) (F3165-5MG) Anti-Myc (sc-40), anti-YAP antibody (sc-101199), anti-hemagglutinin (HA) antibody (901503), anti-YAP (14074S) anti-Thiophosphate ester antibody (ab92670), used for WB or IF have been validated not only by the manufacturers but also in our previous publications (PMID: 25751139, PMID: 30293781, PMID: 32640226, PMID: 31782549) and others(PMID: 33199845, PMID: 27912098, PMID: 26437443).

For the commercial antibodies, anti-MTF1 antibody (NBP1-86380, used for WB and IF), anti-MT1A antibody (NBP1-97493, used for IHC), anti-MTF1 antibody (ab236401, used for IHC), anti-MAP4K4/HGK antibody (A301-502A-M), anti-phospho-MAP4K2 (Ser170) antibody (AB-PK646), anti-SP1 (9389S), anti-CBP (7389S), and anti-C/EBPalpha (8178T), anti-cleaved caspase-3 (9579S), anti-p300 (sc-585), have been validated by the manufacturers (validation results can be found in their websites) and/or previous other people's publications(PMID: 24529376, PMID: 26437443).

The homemade antibodies, anti-MBP, anti-GST, anti-YAP, anti-AMOTL2, were validated and used in our previous publications (PMID: 26456820, PMID: 21187284, PMID: 25751139, PMID: 3029378); the anti-phospho-MTF1 (Ser152) antibody was verified by WB using corresponding site mutation constructs and/or displaying the correct expression pattern between different treatments (e.g., kinase activating- or inactivating- stimuli, kinase KO cells) and IHC to evaluate its correct cellular localization under different treatments.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T (a female cell line, ATCC: CRL-3216), Hep3B (a male cell line, ATCC: HB-8064), MCF10A (a female cell line, ATCC: CRL-10317) and HeLa (a female cell line, ATCC: CCL-2) cell lines were purchased from ATCC and kindly provided by Dr. Junjie Chen (MD Anderson Cancer Center). HEK293A (a female cell line, Thermo Fisher Scientific: R70507) cells were kindly provided by Dr. Jae-Il Park (MD Anderson Cancer Center). MCF10 DCIS cells (a female cell line) were kindly provided by Dr. Jing Yang (University of California, San Diego).
Authentication	No additional authentication was used for the cell lines.
Mycoplasma contamination	All the cell lines used in this study were tested negative by PCR for mycoplasma.
Commonly misidentified lines (See ICLAC register)	None of the cell lines used in this study are listed in ICLAC.

Animals and other organisms

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

Laboratory animals	Five-week-old female C57BL/6 mice were purchased from the Jackson Laboratory and used in this study. Mice were maintained in the University Laboratory Animal Resources (ULAR) Facility of University of California, Irvine under 12-hour light/12-hour dark cycle (on at 6:30 am/off at 6:30 pm) with temperature of 72 ^{o}F ± 2 and 30-70% humidity. 7-day old adult Heterozygous mats Drosophila mutant (stock number 18115), homozygous mtf1 Drosophila mutant (stock number 9241) , wild type Drosophila were obtained from the Bloomington Drosophila Stock Center at Indiana University and used in this study.
Wild animals	No wild animals were used in this study.
Field-collected samples	No filed-collected samples were used in this study.
Ethics oversight	The mouse Cd-intoxication experiments were approved by the Institutional Animal Care and Use Committee (IACUC) and Environmental Health and Safety (EH&S) of University of California, Irvine, and performed under veterinary supervision. The approved IACUC protocol number is AUP-19-113.

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