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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	ImageJ was used for quantification of immunoblot intensity and Metamorph v6.3 software was used to analyze immunostaining images. Microsoft Excel was used to analyze statistical data and draw graphs in the study., Photoshops CS2 or CC 2019 was used to crop images from unprocessed gel images. MSConvert, Mascot search enging 2.2.07, Scaffold software v4.3.2, and Protein Prophet algorithm were used to analyzed the mass spectrometry data.
Data analysis	We did not analyze any commercial or open source data for this study.

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 upon request. 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

Mass spectrometry data have been deposited in ProteomeXchange with the primary accession code PXD012463.
Source data for Fig. 1a, 1b, 1c, 1d, 1e, 2c, 2e, 2g, 3a, 3b, 3e, 3g, 5a, 5b, 5c, 5d, 5f, 5g, 6g, 6i, 7a, 7b, 7c, 7e, 8a, 8c, 8d, 8e, and Supplementary Fig. 1a, 2d, 3h, 3m, 4g, 4i, 4k, 5b, 5d, 5f, 6a, 6d, 7b, 7e, 8b, 8c, 8d have been provided as Supplementary Table 1. All other data supporting the findings of this study are available from the corresponding author on reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Each experiment was repeated independently at least three times and sample sizes and number of repeats are defined in each figure legends. Sample size was determined based on similar studies.
Data exclusions	For the RNAi-based knockdown experiments, knockdown efficiency was measured by quantifying immunoblots and experiments with at least 80% of knockdown efficiency were used for further analysis. Experiments with less than 80% knockdown efficiency were excluded. These exclusion criteria were also used in previous studies (Choi et al., Agonist-stimulated phosphatidylinositol3,4,5-trisphosphate generation by scaffolded phosphoinositide kinases, Nature Cell Biology, 2016; Monteleon et al., IQGAP1 and IQGAP3 serve individually essential roles in normal epidermal homeostasis and tumor progression, Journal of Investigative Dermatology, 2015).
Replication	Each experiment was repeated independently at least three times and sample sizes and number of repeats are defined in each figure legends. All of the experimental findings were reliably reproduced and the data exclusion criteria is described above.
Randomization	No randomization was used in this study as no animal or human research was used.
Blinding	All investigators were blinded during data collection and analysis.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants

Methods

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

Antibodies

Antibodies used

Monoclonal antibodies against p53 (clone DO1), HSP70 (clone W27), HSP27 (clone F-4), MDM2 (clone SMP14, Santa Cruz Biotechnology), p53 (clone 1C12), HSP90 (clone C45G5), HSP27 (clone D6W5V), HA tag (clone 6E2), Myc tag (clone 9B11), MEK1/2 (clone D1A5), Flag tag (clone D6W5B), p110alpha (clone C73F8), PIPKIIalpha (clone D83C1, Cell Signaling Technology), alphaB-Crystallin (clone 1B6.1-3G4, Enzo Lifesciences), actin (clone C4, MP Biomedicals), GST tag (clone RPN1236V, GE Healthcare), His tag (clone HIS.H8, Sigma Aldrich) and polyclonal antibody against Lamin A/C (2032), alphaB-Crystallin (8851), PIPKIalpha (9693), PIPKIIalpha (3296), PIPKIIbeta (9694, Cell Signaling Technology), and HSP27 (ADISPA-801, Enzo Lifesciences) were used for this study. PI4,5P2 antibody (clone KT10)11 was a kind gift from Kiyoko Fukami (Tokyo University of Pharmacy and Life Sciences). For conventional immunostaining and PLA analysis of phosphoinositides, anti-PI3P (Z-P003), -PI4P (Z-P004), -PI3,4P2 (Z-P034), PI4,5P2 (P-Z045), and PI3,4,5P3 (Z-P345) antibodies were purchased from Echelon Biosciences. For immunoblotting analyses, antibodies were diluted in a 1:1000 ratio except for p53 (clone DO1, 1:5000 dilution) and actin (clone C4, 1:500,000 dilution). For immunostaining analyses and proximity ligation assay (PLA), antibodies were diluted in a 1:100 ratio. Nuclear membrane (anti-phosphatidylserine antibody, clone 1H6, EMD Millipore, 1:500) and nuclear speckle (anti-SC-35 antibody, BD Pharmingen, 1:100) markers were used to examine subnuclear regions.

Validation

PIPKIalpha and PIPKIgamma antibodies produced in Dr. Anderson's laboratory were validated by intensive biochemical studies. For example, PIPKIalpha can detect recombinant PIPKIalpha protein but cannot detect recombinant PIPKIgamma protein by immunoblotting. PIPKIalpha antibody used in the immunostaining study was validated in the previous study (J Biol Chem, 278, 23036-23045, 2003; Nature, 451, 1013-1017, 2008). Briefly, PIPKIalpha signal was detected in the plasma membrane and the nucleus and the signal was reduced by PIPKIalpha knockdown by RNAi. Validation of PIPKIalpha, PIPKIgamma, PIPKIIalpha, and PIPKIIbeta for immunoblotting was done using knockout or knockdown cells (Fig. 1a, 1d, and Supplementary Fig. 1a).Validation of p53 (DO1 clone) antibody for immunoblotting and immunostaining was done using p53-null cell line (H1299 and PC3) as in Fig. 2d, 3d, 3f,4a, 4b, and Supplementary Fig. 3b.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

MDA-MB-231, T47D, MCF7, MCF10A, Hs578Bst, Hs578T, DU-145, BT-20, BT-474, BT-549, LNCaP, A431, SkBr3, GILM2, PC3, H1299, HEK293, A549, HCT116, and U2OS cells were purchased from ATCC and maintained in DMEM supplemented with 10% fetal bovine serum (Gibco). MCF10A1 and Hs578Bst2 cells were maintained as described. All the cell lines used in this study are routinely tested for mycoplasma contamination and mycoplasma negative cells were used in the study. None of the cell lines used in this study is listed in the database of commonly misidentified cell lines maintained by ICLAC.

Authentication

We used cell lines that were directly purchase from ATCC and we truthfully used each cell line based on authentication done by ATCC.

Mycoplasma contamination

All the cell lines used in this study are routinely tested for mycoplasma contamination and they were mycoplasma negative.

Commonly misidentified lines
(See ICLAC register)

None of the cell lines used in this study is listed in the database of commonly misidentified cell lines maintained by ICLAC.