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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees and the Editorial Policy Checklist.

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	*Provide a description of all commercial and custom code used to collect the data in this study, specifying the version used OR state that no software was used.*
Data analysis	Graph Prism software

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

Provide your data availability statement here.

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

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	Sizes were defined to have sufficient statistical power
Data exclusions	No data exclusion
Replication	All experiments were performed at least four times and in duplicate
Randomization	Mice were randomly assigned to placebo or treatment
Blinding	All experiments were analyzed blindly

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☐ Unique materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☐	☒ Research animals
☐	☒ Human research participants

Unique materials

Obtaining unique materials: *Describe any restrictions on the availability of unique materials OR confirm that all unique materials used are readily available from the authors or from standard commercial sources (and specify these sources).*

Antibodies

Antibodies used:

Paraffin-embedded kidney sections (4- m) were incubated with anti-P-AKT (Ser473) antibody (Cell Signaling Technology, ref# 4060, dilution 1:100), anti-P-S6RP antibody (Cell Signaling Technology, ref# 5364, dilution 1:100), anti- -smooth muscle cell antibody (Sigma Aldrich, ref# A5228, dilution 1:100), anti-CD34 antibody (eBioscience, ref# 14-0341, dilution 1:100), anti-CD31 antibody (Dianova, ref# Dia-310, dilution 1:30) and anti-podoplanin antibody (Agilent, ref#M3619, dilution 1:50).
Western blots were performed as previously described30. Briefly, protein extracts from the liver, muscles, heart, kidneys and fibroblasts were resolved by SDS-PAGE before being transferred onto the appropriate membrane and incubated with anti-P-AKT (Ser473) antibody (Cell Signaling Technology, ref# 4060, dilution 1:1000), anti-P-AKT (Thr308) antibody (Cell Signaling Technology, ref# 13038, dilution 1:1000), anti- AKT antibody (Cell Signaling Technology, ref# 9272, dilution 1:1000), anti-P-S6RP antibody (Cell Signaling Technology, ref# 5364, dilution 1:1000), anti-p110 (Cell Signaling Technology, ref# 4249, dilution 1:1000), anti-LYVE-1 (R&D Systems, ref# AF2125, dilution 1:1000), anti-P-p44/42 antibody (Cell Signaling Technology, ref# 4370, dilution 1:1000), anti-p44/42 (Thr202/Tyr204) antibody (Cell Signaling Technology, ref# 9102, dilution 1:1000), anti-P-p38 (Thr180/Tyr182) antibody (Cell Signaling Technology, ref# 9216, dilution 1:1000), anti-p38 antibody (Cell Signaling Technology, ref# 8690, dilution 1:1000), anti-GFP antibody (Abcam, ref# ab13970, dilution 1:1000), anti-GAPDH (Merck Millipore, ref#374, dilution 1:1000) or anti- actin antibody (Sigma-Aldrich, ref#A2228, dilution 1:1000), followed by the appropriate peroxidase-conjugated secondary antibody (dilution 1:10000).

Validation: *Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Research animals

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

Animals/animal-derived materials	For this study, we interbred homozygous R26StopFLP110* (Stock# 012343) and heterozygous CAGGCre-ERTM (Stock# 004682) mice on the C57BL/6 background obtained from Jackson Laboratories. We obtained R26StopFLP110*+/- x CAGGCre-ERTM+ mice (referred here as PIK3CACAGG-CreER mice) and R26StopFLP110*+/+ x CAGGCre-ERTM- mice (referred here as PIK3CAWT mice). We used the p110* construction published by Klippel A. et al17 (Supplementary Fig.1). The p110* protein is a constitutively active chimera that contains the iSH2 domain of p85 fused to the NH2-terminus of p110 via a flexible glycine-linker. To generate tissue-specific p110*-transgenic mice, a cloned loxP-flanked neoR-stop cassette was inserted into a modified version of pROSA26-1 followed by the cDNA encoding p110* and then a frt-flanked IRES-EGFP cassette and a bovine polyadenylation sequence (R26StopFLP110*)16. Animals were fed ad libitum and housed at a constant ambient temperature in a 12-hour light cycle. Animal procedures were approved by the "Services Vétérinaires de la Préfecture de Police de Paris" Departmental Director and by the ethical committee of the Paris Descartes University. In the first study, a single dose of tamoxifen (40 mg.kg-1) was administered through oral gavage when the mice were at 21 days of age. For the survival studies, the mice were followed daily after tamoxifen gavage (PIK3CAWT n=16 and PIK3CACAGG-CreER n=16). For the preventive studies, the mice were treated with the PI3KCA inhibitor, BYL719 (MedChem Express; 50 mg.kg-1 in 0.5% carboxymethylcellulose (Sigma Aldrich), daily p.o.) (n=16) or vehicle (0.5% carboxymethylcellulose (Sigma Aldrich), daily p.o.) (n=16). For the therapeutic studies, the mice were treated with the PI3KCA inhibitor, BYL719 (MedChem Express; 50 mg.kg-1 in 0.5% carboxymethylcellulose (Sigma Aldrich), daily p.o.) (n=12) or vehicle (0.5% carboxymethylcellulose (Sigma Aldrich), daily p.o.) (n=12). Treatment was started at the same time of tamoxifen gavage, for the preventive study, or seven days after, for the therapeutic study. In the second study, a single dose of tamoxifen (4 mg.kg-1) was administered through oral gavage when the mice were at 21 days of age (PIK3CACAGG-CreER n=28). Ten mice were sacrificed at approximately 1 month post tamoxifen gavage when tumors reached a certain volume for tissues examination. Once gross morphological abnormalities were visible, eighteen mice were treated with BYL719 during 15 days and treatment was stopped once macroscopic lesions disappeared to follow their phenotype. In the third study, a single dose of tamoxifen (40 mg.kg-1) was administered through oral gavage when the mice were at 21 days of age and then were treated with daily intraperitoneal injection of rapamycin (MedChem Express, ref#HY-10219) (PIK3CACAGG-CreER n=7) or vehicle (PIK3CACAGG-CreER n=7) during 30 days. Rapamycin was dissolved to a final concentration of 0.5 mg.ml-1 in absolute ethanol dissolved further in 5% polyethylene glycol (PEG-400) and 5% Tween 80 in PBS and used for intraperitoneal injection at 4 mg.kg-1. All mice treated with rapamycin or vehicle were then sacrificed for tissues examination. In the fourth study, a single dose of tamoxifen (4 mg.kg-1) was administered through oral gavage when the mice were at 21 days of age (PIK3CACAGG-CreER n=6). Once gross morphological abnormalities were visible (approximately 30 days later), all the mice were treated with daily intraperitoneal injection of rapamycin (MedChem Express, ref#HY-10219) during 30 days. Rapamycin was dissolved to a final concentration of 0.5 mg/ml in absolute ethanol dissolved further in 5% polyethylene glycol (PEG-400) and 5% Tween 80 in PBS and used for intraperitoneal injection at 4 mg.kg-1.

Human research participants

Policy information about studies involving human research participants

Population characteristics	The study was conducted on 19 patients, 4 adults and 15 children, followed at Necker hospital. This protocol was approved by the "Agence Nationale de Sécurité du Médicament et des Produits de Santé" (ANSM, authorizations n°: 553984-986, 584018, 585881-586135, 585464, 585465, 585467, 585880, 586136, 585463, 596229, 588018, 587904, 587896-912, 587908, 587905, 587910, 585458, 595374, 587899) and informed written consent was obtained from the adult patient and the legal representatives of the child. BYL719 was compassionately offered by Novartis. Adult patients received 250 mg/day and child patients received 50 mg/day. BYL719 was orally delivered every morning before breakfast. Patients were followed at regular intervals: weekly during 8 weeks, every two weeks during 1 month and then monthly. Glycaemia was evaluated daily the first month and then progressively sparse. At all time points, the patients had a physical examination and performance status measurement using the Karnofsky (on a scale from 0 to 100, with lower numbers indicating greater disability) and the ECOG indexes (a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing symptoms)25,26. Growth of the children was monitored at all clinical appointments. Blood sampling (complete blood count, kidney and liver functions, glycated hemoglobin measurement) were performed at each time points. Glycaemia was monitored after all meals over two months and then the monitoring became progressively sparse. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All patients had heart ultrasound before BYL719 and then every 3 months. Magnetic resonance imaging studies were performed before BYL719 introduction and then at 3 and 6 months of treatment. PET-scan were performed before and at 3 months of treatment.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☐	☒ Magnetic resonance imaging

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	Spleens of PIK3CAWT (n=12), PIK3CACAGG-CreER induced with tamoxifen 40 mg.kg-1 (n=6) and PIK3CACAGG-CreER induced with tamoxifen 4 mg.kg-1 (n=6) mice were mechanically disrupted in PBS/SVF 2%. Following dissociation, spleens were filtered, centrifuged and resuspended. Cells were then treated with a FC blocker for 10 min at 4°C (Biolegend, ref# 101302) and fixed/ permeabilized (BD Bioscience, ref# 554714). Cells were labeled with chicken polyclonal anti-GFP antibody (Abcam, ref# ab13970) for 30 min at 4ºC. Subsequently, cells were incubated with Alexa Fluor 647-labeled goat anti-chicken IgY antibody (Abcam, ref# ab150171) for 30 min at 4ºC. A background control incubated only with secondary antibody was also included.
Instrument	Samples were analyzed using GalliosTM Flow Cytometer (Beckman Coulter)
Software	FlowJo software (TreeStar)
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

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

Magnetic resonance imaging

Experimental design

Design type	MRI were performed at the Plateforme IRM, INSERM U970, Centre de recherche cardiovasculaire de Paris. Briefly, MRI were performed under general anesthesia in 4 weeks old female PIK3CAWT (n=6) and PIK3CACAGG-CreER (n=6) mice that received 7 days before a single dose of 40 mg.kg-1 tamoxifen to induce Cre recombination. MRI were then repeated weekly in all mice during 1 month.
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	Whole body MRI
Field strength	*Specify in Tesla*
Sequence & imaging parameters	T1, T2
Area of acquisition	Whole body MRI

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
Normalization template	*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s) Spine, muscles, vessels

Statistic type for inference
(See Eklund et al. 2016)

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).