

## 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
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement
<input checked="" type="checkbox"/>	<input type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
<input checked="" type="checkbox"/>	<input type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of all covariates tested
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input type="checkbox"/>	<input checked="" type="checkbox"/> 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)
<input checked="" type="checkbox"/>	<input type="checkbox"/> For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted <i>Give <math>P</math> values as exact values whenever suitable.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input checked="" type="checkbox"/>	<input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
<input checked="" type="checkbox"/>	<input type="checkbox"/> 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	Topspin 4.1 (Bruker Biospin); MicroCal VP-ITC (Malvern)
Data analysis	MicroCal ITC-ORIGIN Analysis Software (Malvern); PyMOL Molecular Graphics System Version 2.4 (Schrödinger, LLC); TALOS-N (DOI: 10.1007/s10858-013-9741-y); CcpNMR 2.5 ( <a href="https://doi.org/10.1007/s10858-016-0060-y">https://doi.org/10.1007/s10858-016-0060-y</a> ); AmberTools21 ( <a href="https://ambermd.org">https://ambermd.org</a> ); matplotlib ( <a href="http://dx.doi.org/10.1109/MCSE.2007.55">http://dx.doi.org/10.1109/MCSE.2007.55</a> ); MDAnalysis ( <a href="https://doi.org/10.1002/jcc.21787">https://doi.org/10.1002/jcc.21787</a> ); BitQt ( <a href="https://doi.org/10.1093/bioinformatics/btab595">https://doi.org/10.1093/bioinformatics/btab595</a> ); ARIA/CNS ( <a href="https://doi.org/10.1093/bioinformatics/19.2.315">https://doi.org/10.1093/bioinformatics/19.2.315</a> )

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](#)

Molecular Dynamic data has been submitted to Zenodo (<https://zenodo.org/doi/10.5281/zenodo.10963887>); The assignment of FOXO4FH, FOXO4CR3, p53TAD2 ,p531-94 and p53DBD had already been submitted to the BMRB under the accession numbers 50398, 50402, 51125, 51124 and 51753, respectively.

Resonance assignments of FOXO4-LRI was submitted to the BRMB under the accession number 52458. The BMRB files corresponding to Figures 1c-f, 2b-c, 4b-d, 5b, 6c and Supplementary Figures 3b-d, 7e-g have been submitted and are waiting for approval.

## Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	N/A
Reporting on race, ethnicity, or other socially relevant groupings	N/A
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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

## 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](https://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 sample size calculation was performed (in vitro study)
Data exclusions	No data was excluded
Replication	Most ITC measurements were performed three times (technical replicates) and results are presented as mean. Pull-down assays were performed in triplicates. All NMR measurements were performed only once.
Randomization	Not relevant to our study (in vitro study, technical replicates)
Blinding	Not relevant to our study (in vitro study, technical replicates)

## 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	Included in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

### Methods

n/a	Included in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

## Antibodies

Antibodies used	Pp53 polyclonal antibody (rabbit, 1:3000, Cat # 10442-1-AP, Lot # 00135720, Proteintech); goat-anti rabbit HRP conjugate (goat, 1:10000, Cat # 1858415, Lot # HG106488, Pierce)
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Validation

The suppliers validated the used antibodies.

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

p53 mutant human TERT-immortalized retinal pigment epithelial 1 (RPE1) cells (RPE1 TP53<sup>-/-</sup>; denoted RPE-1 p53KO) cells were kindly provided by Joanna Loizou (CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria)

Authentication

The RPE-1 cell lines were re-validated by STR profiling.

Mycoplasma contamination

The cell line was tested negative for mycoplasma contamination.

Commonly misidentified lines  
(See [ICLAC](#) register)

N/A (RPE-1 cells are not among the misidentified cell lines)

## Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A