

## 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](#).

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.

For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

### 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** Echo MRI body composition software 2008.01.18M, NIS-Elements BR 3.2, SoftMax Pro 5.4, comprehensive lab animal monitoring system (CLAMS) OxyMax for Windows v5.64, QuantStudio5 Design and Analysis software v1.5.0, Image Lab software 5.2.1.

**Data analysis** FastQC, version 0.11.5 (Babraham Bioinformatics, Cambridge, UK), STAR v2.5.3a, HOMER v4.10, edgeR v3.26.7, R 3.6.1, DESeq2 v1.24.0, pheatmap v1.0.12, ggplot2 v3.3.2, gplots v3.0.1.1, RColorBrewer v1.1-2, VennDiagram v1.6.20, Graphpad Prism 10 for Mac OS X version 10.1.1, Microsoft Excel 16.78, SoftMax Pro 5.4, QuantStudio5 Design and Analysis software v1.5.0, Image Lab software 5.2.1, Adobe Photoshop CC 2015 and/or Adobe Photoshop 2019.

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](#)

RNAseq data has been deposited to GEO under accession code GSE178878. All other data are available in the manuscript, extended data, supplementary materials and source data files.

## 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://www.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

Sample sizes were determined using previously published protocols. Power analyses showed the appropriate sample sizes to use for 80% power to detect an estimated detectable effect size, assuming a 5% significance level and a two-sided test.

Data exclusions

Figure 1 - Troponin I measurements. We had to estimate the appropriate amount to dilute samples for the ELISA. Four uninfected young serum samples and one young surviving infected serum sample were diluted below the limit of detection. We did not have enough serum for these samples to rerun more concentrated, so we omitted these samples from the analysis. Extended Data Figure 4b-f and h-j: pathologist flagged one young surviving and 3 young dying slides as having artifacts present that can compromise interpretations and one young surviving and two young dying slides as having severe artifacts present and slides poor quality therefore these were omitted from data plots. Extended Data Figure 7h: pathologist flagged one lung from vehicle surviving mouse as possible artifact. This sample was omitted. Extended Data 8i-p: pathologist flagged one wildtype infected slide as having artifacts and was not scored. We still had sufficient sample sizes even with these samples omitted.

Replication

Experiments were performed with biologically independent animals for each condition and experiments were repeated independently as indicated in the figure legends.

Randomization

Allocation was random within sex- and age-matched cohorts. Within each genotype, mice of the same sex and age were randomly assigned to experimental groups. Littermates were used whenever possible. Independent experimental replicates included mice from different litters and cages and were performed on different days, allowing potential litter, cage or day effects to be identified. Potential confounding factors were controlled through experimental design and replication.

Blinding

Blinding was not possible for animal infection experiments because disease outcomes (e.g. survival and visible morbidity) were readily apparent to investigators. For quantitative assays including ELISAs, qPCR, western blots, blood chemistry, histopathology, tissue weights, the individuals performing the assays/analyses were blinded to group allocation. Data for ELISAs, qPCRs, blood chemistry were collected by machine-based, unbiased, quantitative means.

# 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                                           |
|-------------------------------------|-----------------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines                  |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology          |
| <input type="checkbox"/>            | <input checked="" 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                                 | Involved 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 | GAPDH (14C10) Rabbit mAb Cell Signaling 21185 (1:1000), Phospho-FoxO1 (Thr24)/FoxO3a (Thr32) Antibody Cell Signaling 94645 (1:1000), Phospho-FoxO1 (Ser256) Antibody Cell Signaling 9461 (1:1000), FoxO1 (C29H4) Rabbit mAb Cell Signaling 28805 (1:1000), Anti-rabbit IgG HRP-linked Ab Cell Signaling 70745 (1:3000).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Validation      | <p>All primary antibodies were obtained from Cell Signaling Technology and have been validated by the manufacturer for the indicated applications and species. Specifically, the following antibodies are validated for immunoblotting in mouse and rat samples according to the manufacturer's website:</p> <p>GAPDH (14C10) Rabbit mAb (#21185) - validated for western blot, mouse, rat and human.</p> <p>Phospho-FoxO1 (Thr24/FoxO3a (Thr32) antibody (#94645) - validated for western blot, mouse, rat and human.</p> <p>Phospho-FoxO1 (Ser256) antibody (#9461) - validated for western blot, mouse, rat and human.</p> <p>FoxO1 (C29H4) Rabbit mAb (#28805) - validated for western blot, mouse, rat and human.</p> <p>Anti-rabbit IgG, HRP-linked antibody (#70745) - validated for use as a secondary antibody in western blot applications.</p> <p>All antibodies were used at the dilutions recommended by the manufacturer and produced bands at the expected molecular weights in our samples, consistent with the manufacturer's validation data.</p> |

## Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

|                         |                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals      | <p>CS 7BL/6 Jackson Laboratories 000664</p> <p>Trim63<sup>-/-</sup> and Trim63<sup>+/-</sup>, Trim63<sup>-/-</sup> this study</p> <p>For experiments with young animals 12-14 week old animals were used</p> <p>For experiments with old animals 72-76 week old animals were used.</p> <p>Mice were housed with a 12hr light/dark cycle, humidity 30-70% and temperature 64-79 deg F.</p> |
| Wild animals            | No wild animals were used in this study.                                                                                                                                                                                                                                                                                                                                                  |
| Reporting on sex        | Females were used for all experiments.                                                                                                                                                                                                                                                                                                                                                    |
| Field-collected samples | No field collected samples were used in this study.                                                                                                                                                                                                                                                                                                                                       |
| Ethics oversight        | All experiments were performed in our AAALAC-certified vivarium, with approval from The Salk Institute Animal Care and Use committee.                                                                                                                                                                                                                                                     |

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

## Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A

