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 wherever 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 | Commercially available software was used and is stated in the Materials and Methods |
| Data analysis   | Commercially available software was used and is stated in the Materials and Methods |

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 datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender

Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data where this information has been collected, and consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.

Population characteristics

Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write “See above.”

Recruitment

Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.

Ethics oversight

Identify the organization(s) that approved the study protocol.

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

Life sciences study design

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

- Sample size
  Sample size followed that of similar studies from our and other labs in previous publications. Replications show consistent results.

- Data exclusions
  No data was excluded

- Replication
  At least 3 or more independent mice (as indicated in Figure legends) were analyzed in independent experiment’s (e.g. on different days). Each experiment itself was carried out at least in triplicates. For Hc, IF and W8, representative data is shown. For quantifications, all data points generated were included in the analysis and shown in the graphs.

- Randomization
  Test samples were compared to corresponding Crti littermates. We previously analyzed the key liver parameters also analyzed in this study in several different possible control strain cohorts and found no significant difference, justifying the selection of controls.

- Blinding
  Investigators were blinded to group allocation

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

| r/a | Involved in the study |
|-----|-----------------------|
| X   | Antibodies            |
| X   | Eukaryotic cell lines |
| X   | Palaeontology and archaeology |
| X   | Animals and other organisms |
| X   | Clinical data         |
| X   | Dual use research of concern |

### Methods

| r/a | Involved in the study |
|-----|-----------------------|
| X   | ChIP-seq              |
| X   | Flow cytometry        |
| X   | MRI-based neuroimaging |
Antibodies

| Antibodies used | Antibodies used are listed in Materials and Methods with source and catalogue number |
|-----------------|-----------------------------------------------------------------------------------|
| Validation      | Validation is based on validation statements on manufacturers’ website and relevant citations using the respective antibodies |

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 | Species, strains and age of the mice are stated in the Materials and Methods |
|--------------------|--------------------------------------------------------------------------------|
| Wild animals       | N.A.                                                                              |
| Reporting on sex   | Data from male animals are shown to exclude female hormonal cycle influences. However, similar results were obtained for female mice where analyzed. This is stated in the manuscript. |
| Field-collected samples | N.A.                                                                              |
| Ethics oversight   | A*STAR IACUC, Protocol #201558. Full approval information provided in Materials and Methods |

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