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# Life Sciences Reporting Summary

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For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees 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.

## Experimental design

1. Sample size

   Describe how sample size was determined.

   Previous studies and pilot experiments form the basis of power calculations for the various studies. Depending on the experiment, calculations indicated that 3-12 mice per group would enable the testing of our hypotheses based on an expected 25-30% coefficient of variation and an 80% chance of detecting a 33% difference in the key specified endpoints ( P =0.05)

2. Data exclusions

   Describe any data exclusions.

   Pre-specified exclusion criteria were weight loss>10% of initial body weight or signs of illness or injury requiring euthanasia. According to these pre-specified criteria, the maximum number of mice removed before analysis was 3, but more typically 0-2.

3. Replication

   Describe the measures taken to verify the reproducibility of the experimental findings.

   All experiments were reproducible as assessed in multiple wells of cells, tissue samples or mice. We did not have cases of irreproducibility. Please note that the bar graphs depicting spectral counts (Ext. Data Fig. 2g and Ext. Data Fig. 8a) simply represent a single MS/MS experiment, and likewise the FPLC fractions (Ext. Data Fig. 2f and Ext. Data Fig. 7c) were screened using technical duplicates, but all of these data were subjected to extensive reproducibility in all the subsequent biological assays related to these data.

4. Randomization

   Describe how samples/organisms/participants were allocated into experimental groups.

   Mice of the same age and similar weight were randomly assigned to experimental and control groups. On occasion, we analyzed a subset of mice for a particular parameter, and the subset was chosen randomly from a full cohort.

5. Blinding

   Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

   The investigators were not blinded during cell and mouse experiment assays.

Note: all in vivo studies must report how sample size was determined and whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

| n/a | Confirmed |
|---|---|
| ☐ | ☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.) |
| ☐ | ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ A statement indicating how many times each experiment was replicated |
| ☐ | ☒ The statistical test(s) used and whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☐ | ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons |
| ☐ | ☒ Test values indicating whether an effect is present<br>*Provide confidence intervals or give results of significance tests (e.g. P values) as exact values whenever appropriate and with effect sizes noted.* |
| ☐ | ☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range) |
| ☐ | ☒ Clearly defined error bars in all relevant figure captions (with explicit mention of central tendency and variation) |

*See the web collection on statistics for biologists for further resources and guidance.*

## Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.

Image J for density ratio measurements; Proteome Discoverer 1.4

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

## Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a third party.

No restrictions--all mutant mice are commercially available or available from the labs indicated in the manuscript, and the methods for GeRP construction is published.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

The source and catalogue number of all antibodies appear in Methods. Antibodies were validated by showing lack of signal after knockout or siRNA or by a single major band at the proper MW on immunoblot.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

N/A

b. Describe the method of cell line authentication used.

N/A

c. Report whether the cell lines were tested for mycoplasma contamination.

N/A

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.

N/A

## Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide all relevant details on animals and/or animal-derived materials used in the study.

All details appear under "Mouse experiments" section in methods

Policy information about studies involving human research participants

12. Description of human research participants

| | |
|---|---|
| Describe the covariate-relevant population characteristics of the human research participants. | N/A |