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Corresponding author(s): Beth Levine

Reporting Summary

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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	NO software was used.
Data analysis	The ImageJ software was used to outline and measure areas. GraphPad Prism 7 was used to represent data in graphs and for the statistical analyses of the data. The online application Oasis 2 was used for the analyses of maximal lifespan.

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

Full scans for all western blots are provided in Supplementary Fig. 1. Source data for all graphs in this manuscript have been provided. All other data are available from the corresponding authors on reasonable request.

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	For western blot analyses and autophagy analyses, three mice per genotype were used for each analysis. This sample size is sufficient to determine whether there is a biologically meaningful difference between different genotypes, given the known mouse-to-mouse variation in autophagy assessments using GFP-LC3 transgenic animals in previous studies published over the past decade. For lifespan analyses, the maximum number of wild-type and mutant littermates born within a six-month period were used. This number included more than 30 mice per gender per genotype, which is generally accepted in mammalian aging research as a sample size sufficient for proper comparison and minimal statistical analyses was chosen for western blots. For phenotypic analyses of WT and KI mice, age-matched littermates of WT (n=28) and KI mice (n=55) were sacrificed at 20 months and analyzed by a pathologist blinded to genotype for tumorigenesis. The kidneys and hearts of all mice without tumors were further analyzed. The sample size for hearts and kidneys differs somewhat, as mice with heart or kidney sections that were inadvertently sectioned at a different level than the designed regions were excluded prior to analyses. The maximal number of fields that would cover the tissue was used for quantitations when images were taken for further analysis. Since it is well-established that Klotho hypomorphic mice die within 12 weeks, a smaller sample size was determined to be sufficient to assess the effects of the Becn1 F121A mutation on premature aging in Klotho deficiency. The precise number of animals used is indicated below in response to question 11.
Data exclusions	No data were excluded.
Replication	All attempts at replication were successful.
Randomization	This study primarily involves the comparison of mice with different genotypes, rather than randomization into different treatment groups. Therefore, experimental groups consisted of littermates of different genotypes. The only need for allocation into experimental groups was for selecting GFP-LC3 mice to be treated with PBS or with chloroquine in Fig. 1. For these studies, six mice were genotype were randomly assigned to received either PBS (n=3) or chloroquine (n=3).
Blinding	All data acquisition and analysis was performed by investigators blinded to experimental group.

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

Antibodies

Antibodies used	The antibody anti-beclin 1 H300 from Santa Cruz (sc-7382) was used at 1:500 dilution. The antibody anti-Bcl-2 C-2 from Santa Cruz (sc-7382) was used at 1:100 dilution. The antibody anti-Klotho KM2076 from transgenic Inc. (KO603) was used at 1:1000 dilution. The antibody anti-beta actin C-4 from Santa Cruz (sc-47778) was used at 1:5000 dilution. The antibody anti-p62 from Progen (GP62-C) was used at 1:2000 dilution. The antibody anti-LC3B from sigma (L75430) was used at 1:10000 dilution for western blot assays and the antibody anti-LC3B 5F10 from Enzo (ALX-803-080-C100) was used at 1:40 dilution for

immunofluorescence staining. The antibody anti-active Caspase-3 antibody from abcam (ab2302) was used at 1:20 dilution. All antibodies validation are available on the manufacturers' websites.

Validation

All antibodies validation are available on the manufacturers' websites.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	The Hela cell line from ATCC was used.
Authentication	The cell line was authenticated by ATCC Cell Line Authentication Service.
Mycoplasma contamination	The cell line tested negative for mycoplasma contamination by PCR analysis.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Research animals

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

Animals/animal-derived materials	Becn1F121A/F121A mice were generated as described in reference 18 and backcrossed for more than 12 generations to C57BL/6J mice (Jackson Laboratories). Becn1WT/WT (WT) and Becn1F121A/F121A (KI) littermate mice were crossed with GFP-LC3 transgenic animals described in reference 13, in a pure C57BL/6J background . Klotho HM hypomorphic mice (known as kl/kl mice) were in a controlled C57BL/6J and 129 mixed background. GFP-LC3 puncta quatification was performed on on 3 females per group. Survival experiments had 31 WT female, 43 KI female, 37 WT male and 59 KI male mice. Young mice were 2 month-old and 3 males and 3 females of each genotype (WT and KI) were used for all experiments. The approximate age of the aged mice used for histopathological analyses was 20 months-old. The analyses of the heart were performed on 19 WT mice (7 females and 12 males) and 23 KI mice (13 females and 10 males). The analyses of the kidney were performed on 20 WT mice (8 females and 12 males) and 26 KI mice (13 females and 13 males). As mentionned in the figure, Klotho survival experiments had 23 WT, 23 KI, 19 Klotho HM, 26 KI/Klotho HM female mice and 12 WT, 21 KI, 18 Klotho HM, 25 KI/Klotho HM male mice. Body weights were measured for 12 mice per gender for each genotype.

Method-specific reporting

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