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☐ Initial submission ☒ Revised version ☐ Final submission

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.

Experimental design

1. Sample size

Describe how sample size was determined.

All cell culture experiments requiring statistical analysis were performed at least 3 times as indicated in the figure legends. Power analysis were used to predetermine the sample size in case of in vivo studies. For animal experiments requiring statistical analysis we used at least 5 animals per group. See specific figure legends (page 20-22) and suppl. figure legends. The first paper describing the beta-amyloid seeding method in similar mouse models (intrahippocampal beta amyloid injections) reported the use of 3 to 5 mice per group (Meyer-Luehmann et al. Science, 2006). For animal experiments requiring statistical analysis we used at least 5 animals per group. See figure legends for specific n numbers (page 20-22) and suppl. figure legends.

2. Data exclusions

Describe any data exclusions.

All animals were healthy and generated specifically for the experiments described. Animals or samples were excluded from analysis only in the instance of technical failure.

3. Replication

Describe whether the experimental findings were reliably reproduced.

All experiments were reliably reproduced, detailed statistical analysis is provided.

4. Randomization

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

No specific method of randomization was used for generation of samples or in animal experiments. The animals were littermate, and inbred lines were used, where the individual mice were identical, therefore no randomization were needed. The animals were randomly assigned to the experimental conduct (e.g. Morris Water Maze test)

5. Blinding

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

Analysis of data was performed in by blinded researchers.

Note: all studies involving animals and/or human research participants must disclose 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 (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals 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

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.

Graph Pad Prism 6 for Mac OS or R.
FlowJo X 10.0.7 (Ashland, OR, U.S.A.)
Volocity 6.01 software (PerkinElmer, Waltham, Massachusetts, U.S.A.)
Li-COR Image Studio Software (Li-COR, Bad Homburg, Germany)
Chemidoc XRS documentation system (Biorad, Munich, Germany)
Ethovision 3.1(Noldus, Wageningen – The Netherlands)
ImageJ (National Institute of Health)

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 for-profit company.

There are no restrictions on availability of material used for his study.

9. Antibodies

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

- ASC antibodies: BioLegend, San Diego, CA, U.S.A., mAb, 653902, clone TMS-1, and AdipoGen ASC, AL177, AG-25B-0006-C100, Liestal, Switzerland.
- CD11b: rat anti-mouse CD11b, MCA711, Serotec, Oxford, UK.
- 6E10: Aβ anti-human, 6E10, SIG-39320, Covance, Münster, Germany..
- C-terminal APP antibody 140 (CT15) Wahle T. et al. J. Neurosci 26, 12838-12846, 2006
- Insuling degrading enzyme: PC730, Calbiochem, Darmstadt, Germany.
- caspase-1 antibodies: casp-1 clone 4B4.2.1 (gift from Genentech, San Francisco, CA) and a caspase-1 antibody raised in rabbit (gift from Gabriel Nuñez).
- Neprilysin: 56C6, Santa Cruz, Heidelberg, Germany.
- β-actin using A2228, Sigma, Munich, Germany.
- Alexa fluor 488: goat anti-Rat-Alexa Fluor 488, A11006, ThermoFisher, Darmstadt, Germany.
- 82E1 anti-Human Amyloid beta, 10323, Immuno-Biological Laboratories.
- Alexa fluor 488: goat anti-Mouse-Alexa Fluor 488, A-11017, ThermoFisher, Darmstadt, Germany.
- Alexa fluor 594: goat anti-Rabbit-Alexa Fluor 594, A11072-, ThermoFisher, Darmstadt, Germany.

10. Eukaryotic cell lines

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

THP1 cells were aquired from ATCCC,
19.5 iMOs (inflammasome reporter mouse immortalized macrophages): Cell line was generated in the Latz laboratory. NLRP3 deficient bone marrow cells were immortalized using the J2 virus and immortalized macrophages were obtained and retroviral reconstituted with flag tag NLRP3 as well as mCerulean tagged ASC identity. Western Blot confirmed expression of NLRP3 and ASC.

b. Describe the method of cell line authentication used.

19.5 iMOs (inflammasome reporter mouse immortalized macrophages): Cell Identity was ascertained by mRNA transcriptional profiling.

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

Yes, any mycoplasma contamination has been excluded.

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.

Cell lines used are not in ICLAC.

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

APP/PS1 transgenic (The Jackson Laboratory, Bar Harbor, ME, U.S.A., strain #005864), ASC-/- (Millennium Pharmaceuticals, Cambridge, MA, U.S.A.), APP/PS1/ASC-/- animals on the C57Bl/6 genetic background.
C57Bl/6 animals as control.
Only female animals were included at the age of 3, 6, 8 and 12-month.

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.

Only patient-derived brain samples were used. The human tissue was provided by the co-author Dr. Ellen Gelpi from the Neurological Tissue Bank of the biobank of the Hospital Clínic-IDIBAPS, Barcelone, SPAIN. Post mortem brain material from histologically confirmed AD, VD, FTD and CBD cases as well as age-matched controls that had died from non-neurological disease, were derived from the Neurological Tissue Bank of the Biobank of the Hospital Clínic-IDIBAPS. Postmortem times across all cases varied from 3.5-5 hrs. After explantation brain specimen were immediately snap frozen and stored at -80°C until further use. Patients and controls were males and females, 75 ±6 yrs old