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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 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	Flow cytometry was collected by BD FACSLyric. Western blot imaging acquisition was perform by Bio Rad ChemiDoc Imaging System. Real-time PCR was performed using the QuantStudio 12K Flex Real-Time PCR System (Applied Biosystems). CCK8 viability absorbance was mesaured by Tecan Infinite M Nano. Single-cell capture were performed using the microwell-based BD Rhapsody. RNA-seq libraries were sequenced on an Illumina NovaSeq 6000 system.
Data analysis	Flow cytometry data was analyzed with FlowJo Software v10.9 (BD Biosciences). Statistical analyses were performed using Graphpad Prism v9 (Graphpad Software). Single-cell RNA sequencing (scRNA-seq) and bioinformatic analyses were performed using R software (R project) with Seurat package (v5.3.0).

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

scRNA-seq data and code are available at GitHub (https://github.com/anabelgh/hepcasp1-scRNA-seq.git). All the other data are available in the main text or the supplementary materials.

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	not applicable
Reporting on race, ethnicity, or other socially relevant groupings	not applicable
Population characteristics	not applicable
Recruitment	not applicable
Ethics oversight	not applicable

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	No formal sample size calculation was performed. Sample sizes were determined based on previously published studies using comparable HCC models and our own experience with these models. These group sizes are commonly used in the field, and provide statistical power while minimizing the use of animals according with ethical guidelines.
Data exclusions	No data was excluded from the analyses
Replication	Initial in vivo experiments using the western diet + CCl4 model were repeated in two independent cohorts of mice to confirm reproducibility. In vivo experiments employing the orthotopic model were performed once, with at least 4 biological replicates and results supported by strong internal consistency across animals. Single-cell RNA sequencing (scRNA-seq) analyses included 4 biological replicates. Western blot analyses from in vivo samples included 3 or 4 biological replicates. Western blot and immunoprecipitation analyses from HCC cell lines were performed twice or thrice, or performed once but reproduced in two different cell lines (Hepa1-6 and Hep53.4). Flow cytometry analyses from mouse samples included a minimum of 4 biological replicates, with most experiments having 5-6 biological replicates. To increase transparency, quantitative data across the manuscript is presented as scatter dot plot showing individual data points with line at median.
Randomization	Randomization was not applicable for comparisons between wild type and CASP1 deficient mice, since animals were assigned to experimental groups based on genotype. For TBK1 inhibition in vivo, animals were randomized into treatment groups. For inhibitor studies, animals were randomized into treatment groups using a stratified randomization approach based on body weight to ensure balanced group allocation
Blinding	Blinding of investigators during data collection was not possible, since animals were housed in different cages based on genotype. However, data analysis was performed blindly. For in vitro studies, blinding of cell line treatments was not possible; however, all cell lines were treated identically without prior designation

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
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

For western blots. TBK1 (CST #3504; Invitrogen #MA5-42812), STING (CST #50494), p-TBK1 (CST #5483), IRF3 (CST #4302), p-IRF3 (CST #29047), cleaved PARP (CST #94885), p-RIP (CST #53283), p62 (CST #23214), PPARα (Abcam #ab314112), CASP1 (Abcam #ab179515; Novus NB100-56565; Invitrogen #PA5-99390), Vinculin (CST #13901), and β-actin (CST #4967). Secondary antibodies: anti-rabbit (CST #7074), anti-mouse (CST #7076), anti-rabbit IgG light chain (Abcam #ab99687), and Veriblot IP detection reagent (Abcam #ab131366).
For flow cytometry: viability dye (#65-0866-14, Invitrogen) , CD11b (BD #561039, clone M1/70), Ly6C (BD #560593, clone AL-21A8), Ly6G (BD #560602, clone 1A8), CD4 (BD #563050, clone GK1.5), PD-1 (BioLegend #135205, clone 29F.1A12), CD11c (Invitrogen #47-0114-80, clone N418), CD8α (BD #563152, clone 53-6.7), F4/80 (BioLegend #157303, clone QA17A29), MHC-II (Invitrogen #48-5321-80, clone M5/114.15.2), CD44 (Invitrogen #11-0441-82, clone IM7), and CD62L (BD #562910, clone MEL-14). Intracellular staining was performed using the Foxp3/Transcription Factor Staining Buffer Set (Invitrogen) fand anti-TNFα (BioLegend #506328, clone MP6-XT22) and anti-IFNγ (Invitrogen #17-7311-82, clone XMG1.2).

Validation

All the antibodies used are commercially available and have been validated by the manufacturer for their use in the respective application.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

The murine Hep53.4 cells line were purchased from Cytion and Hepa1-6 from DSMZ-German Collection of Microorganisms and Cell Cultures.

Authentication

All cell lines were expanded from internally maintained stocks. Once thawed, cells were cultured for no more than ten passages in a humidified incubator in 5% CO2 and 95% air at 37 C. All cell lines were authenticated based on morphological criteria only.for no more than ten passages in a humidified incubator in 5% CO2 and 95% air at 37 C. All cell lines were authenticated based on morphological criteria only.

Mycoplasma contamination

Cells lines were tested negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used.

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

Wild-type (WT) C57BL/6J and Casp1-/- mice (strain #016621) were originally obtained from The Jackson Laboratory (Bar Harbor, ME) and maintained on a C57BL/6J background. All animals were housed in individually ventilated cages under specific pathogen–free (SPF) conditions at the Animal Facility of the University of Miguel Hernández of Elche (UMH).

Wild animals

No wild animals was used in this study.

Reporting on sex

All mice were males.

Field-collected samples

Not field-collected samples was used in this study

Ethics oversight

All experimental procedures were supervised by the Research Ethics Committee of the UMH and approved by the Office of Agriculture, Rural Development, and Climate Change of the Generalitat Valenciana (approval number 2020/VSC/PEA/0100). All animals received humane care in accordance with the Spanish and European legislations.

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

Plants

Seed stocks	not applicable
Novel plant genotypes	not applicable
Authentication	not applicable

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Livers were perfused with perfusion buffer (Gibco), digested with liver digestion buffer (Gibco), and filtered through a 70-µm cell strainer. The cell suspension was resuspended in 5 mL of 40% isotonic Percoll (Cytiva) and overlaid onto 3 mL of 60% isotonic Percoll. After centrifugation (800g, 20 min, no brake), lymphocytes were collected from the interphase. Red blood cells lysis was performed and then cells were staining in 10% FBS PBS with master mix antibodies for 30 min, 4 degrees at dark. Intracellular staining was performed using the Foxp3/Transcription Factor Staining Buffer Set (Invitrogen).
Instrument	BD FACSLyric Flow Cytometry
Software	Flow cytometry data collection was done with BD FACSuite™ Application and flow cytometry data analysis was done with Flowjo 10.9.0.
Cell population abundance	We did not perform FACS sorting experiments. The relevant abundance of conventional flow cytometry analyses was determined as a percentage. Fluorescence minus one (FMO) and isotype controls were used for each antibody to ensure specificity in all stainings.
Gating strategy	Flow-cytometry analysis used a sequential gating strategy. Cells were first gated on FSC-A and SSC-A to exclude debris, followed by FSC-A/FSC-H gating to select singlets and viability-dye exclusion to retain live cells. For T cell analysis, viable single cells were gated for $CD4^+$ and $CD8^+$ populations, and PD-1 expression was assessed within the $CD4^+$ and $CD8^+$ gates. CD62L/CD44-defined $CD8^+$ T cell subsets were quantified within the $CD8^+$ T cell population. For intracellular cytokine analysis, IFNγ and TNFα expression was assessed within gated $CD8^+$ Tc ell populations after live singlet selection. IFNγ expression was assessed within gated $CD4^+$ T cell populations. For myeloid-cell analysis, viable single cells were gated using CD11b and Ly6G to identify neutrophil and non-neutrophil myeloid populations; $CD11b^+Ly6G^-$ cells were further analysed using Ly6C and MHCII, and macrophages were identified as $CD11b^+F4/80^+$ cells. The same gating strategy was applied consistently across all samples

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.