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Reporting Summary

Nature Research 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 Research 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	Applied Biosystems® 7500 fast and 7500 Real-Time PCR System (7500 v2.3) was used to collect relative gene expression (RQ) values. Visual Sonic Vevo® 2100 system was used for in vivo collection of ultrasound signals of fibrotic livers. Zeiss ZEN 2011 was used to collect confocal images. Image Lab 6.0.1 was used to acquire western blot images. Flow cytometry data were acquired with BD FACSDIVA™ v8.0.1.
Data analysis	Flow cytometry data were analyzed with FlowJo V10. ImageJ 1.48v was used for confocal, western blot, and ultrasound image processing. GraphPad Prism 7.04v was used to analyze the data.

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 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

MicroRNA Data Integration Portal (mirDIP) was used to identify gene targets for exosomal miRNAs and can be accessed with http://ophid.utoronto.ca/mirDIP. The authors declare that the data supporting the findings of this study are available within the paper and its supplementary information files.

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 was determined by power analysis (90% power at 5% significance level).
Data exclusions	No exclusion criteria were incorporated in the design of the experiments for this study.
Replication	All experiments were repeated twice or three times as indicated in figure legends with similar results.
Randomization	Groups in all in vitro experiments were selected randomly. Mice receiving 4-week injections of CCl4 or fed with CDAHFD for 8 weeks were randomized blindly into different treatment groups.
Blinding	The investigator was blinded to the group allocation during the animal experiments and in vitro studies. And all analyses were performed by investigators blinded to the experimental conditions.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	The antibodies used in this study were summarized in Supplementary Table 2. The primers for quantitative PCR used in this study were summarized in Supplementary Table 3.
Validation	All antibodies were verified by the supplier and each lot has been quality tested. All the antibodies used are from commercial sources and have been validated by the vendors. Validation data are available on the manufacturer's website. 1. Alexa Fluor® 488 anti-α-SMA has been validated to be used for immunofluorescent staining and flow cytometric analysis and mentioned species reactivity with mouse. (https://www.thermofisher.com/antibody/product/Alpha-Smooth-Muscle-Actin-Antibody-clone-1A4-Monoclonal/53-9760-82) 2. APC anti-F4/80 has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/apc-anti-mouse-f4-80-antibody-4071) 3. FITC anti-CD68 has been validated to be used for immunofluorescent staining and mentioned species reactivity with human. (https://www.biolegend.com/en-us/products/fitc-anti-human-cd68-antibody-4844) 4. Anti-RXFP1 has been validated to be used for immunofluorescent staining and Western analysis and mentioned species reactivity with mouse and human. (https://www.rndsystems.com/products/human-mouse-rat-relaxin-r1-antibody-933344_mab8898) 5. Anti-CD63 has been validated to be used for immunofluorescent staining and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/purified-anti-mouse-cd63-antibody-7813) 6. Anti-Nur77 has been validated to be used for immunofluorescent staining and Western analysis and mentioned species reactivity with human. (https://www.cellsignal.com/products/primary-antibodies/nur77-d63c5-xp-rabbit-mab/3960) 7. Anti-α-SMA has been validated to be used for immunofluorescent staining and Western analysis and mentioned species reactivity with mouse and human. (https://www.abcam.com/alpha-smooth-muscle-actin-antibody-1a4-ab7817.html) 8. Anti-Collagen I has been validated to be used for Western analysis and mentioned species reactivity with mouse and human. (https://www.abcam.com/collagen-i-antibody-ab34710.html) 9. Anti-PKA has been validated to be used for Western analysis and mentioned species reactivity with mouse. (https://

www.cellsignal.com/products/primary-antibodies/pka-c-a-antibody/4782)
10. Anti-pCREB (Ser133) has been validated to be used for Western analysis and mentioned species reactivity with mouse. (https://www.cellsignal.com/products/primary-antibodies/phospho-creb-ser133-87g3-rabbit-mab/9198)
11. Anti-ASK1 has been validated to be used for Western analysis and mentioned species reactivity with human. (https://www.cellsignal.com/products/primary-antibodies/ask1-antibody/3762)
12. Anti-ASK1 (Thr845) has been validated to be used for Western analysis and mentioned species reactivity with human. (https://www.cellsignal.com/products/primary-antibodies/phospho-ask1-thr845-antibody/3765)
13. GAPDH antibody has been validated to be used for Western analysis and mentioned species reactivity with mouse and human (https://www.scbt.com/p/gapdh-antibody-fl-335)
14. BV510 anti-CD45 has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/brilliant-violet-510-anti-mouse-cd45-antibody-7995)
15. Pacific Blue anti-Ly6G has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/pacific-blue-anti-mouse-ly-6g-antibody-6082?GroupID=GROUP20)
16. PE anti-F4/80 has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/pe-anti-mouse-f4-80-antibody-4068?GroupID=GROUP20)
17. FITC anti-CD11b has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/fitc-anti-mouse-human-cd11b-antibody-347)
18. PE/Cy7 anti-Ly6C has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-us/products/pe-cyanine7-anti-mouse-ly-6c-antibody-6063)
19. Alexa Fluor® 647 anti-Clec4f has been validated to be used for flow cytometric analysis and mentioned species reactivity with mouse. (https://www.biolegend.com/en-gb/products/alexa-fluor-647-anti-mouse-clec4f-antibody-18329)
20. FITC anti-human CD16 has been validated to be used for flow cytometric analysis and mentioned species reactivity with human. (https://www.biolegend.com/en-us/products/fitc-anti-human-cd16-antibody-567)
21. PE anti-human CD14 has been validated to be used for flow cytometric analysis and mentioned species reactivity with human. (https://www.biolegend.com/en-us/products/pe-anti-human-cd14-antibody-12011)
22. APC anti-human CD56 (NCAM) has been validated to be used for flow cytometric analysis and mentioned species reactivity with human. (https://www.biolegend.com/en-us/products/apc-anti-human-cd56-ncam-antibody-9941)
23. PE/Cy7 anti-human CD66b has been validated to be used for flow cytometric analysis and mentioned species reactivity with human. (https://www.biolegend.com/en-us/products/pe-cyanine7-anti-human-cd66b-antibody-12499)
24. Goat anti-rabbit HRP has been validated to be used as a secondary antibody for rabbit primary antibodies for Western analysis. (https://www.abcam.com/goat-rabbit-igg-hl-hrp-ab205718.html)
25. m-IgGκ BP-HRP has been validated to be used as a secondary antibody for mouse primary antibodies for Western analysis. (https://www.scbt.com/p/m-igg-kappa-bp-hrp)
26. Alexa Fluor® 555 Goat anti-Mouse IgG H&L has been validated to be used as a secondary antibody for mouse primary antibodies for immunofluorescence staining. (https://www.abcam.com/goat-mouse-igg-hl-alexa-fluor-555-ab150114.html)

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	LX-2 and HSC-T6 were purchased from Sigma-Aldrich. Human primary hepatic stellate cells were purchased from iXCells Biotechnologies. Fresh human peripheral blood mononuclear cells were purchased from STEMCELL Technologies Inc. L929, Raw264.7, and THP-1 were obtained from Tissue Culture Facility—UNC Lineberger Comprehensive Cancer Center. Human primary bone marrow derived mononuclear cells were purchased from ATCC.
Authentication	None of the cell lines used were authenticated.
Mycoplasma contamination	The cell lines were tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No cell lines used are listed in the database of commonly misidentified cell lines.

Animals and other organisms

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

Laboratory animals	Eight-week-old male C57BL/6 mice were purchased from the Jackson Laboratory. Mice were housed in Specific-Pathogen Free animal facility in ambient temperature (24±2 °C), air humidity 40%–70% and 12 h dark/12 h light cycle.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the filed.
Ethics oversight	All animal handling procedures were approved by the University of North Carolina at Chapel Hill's Institutional Animal Care and Use Committee.

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Liver samples were acquired during hepatic resection surgery. They were from 7 male patients ranging in age from 42 to 65.

Population characteristics	5 samples were from patients with cirrhosis alone and the other 2 were from patients with cirrhosis combined with hepatocellular carcinoma. All subjects give informed consent. All tissue specimens are de-identified.
Recruitment	Eligible patients were invited to participate by one of the investigators or a designee of one of the investigators. If they are willing to participate, the investigator or their designee reviewed the consent form and obtained informed consent. All cirrhosis patients with planned surgery were consented to the liver tissue collection protocol. Patients were approached in clinic by study personnel without relation to age, race, gender, disease stage, or prior therapies. No significant biases appeared to be present.
Ethics oversight	HwaMei Hospital, University of Chinese Academy of Sciences

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

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	Sample preparation listed in Online Methods, 'Flow cytometry assay' section.
Instrument	BD LSR II, LSRFortessa, FACSArio II
Software	BD FACSDIVA™ (Version 8.0.1)
Cell population abundance	Cell count of 20,000 or 8,000,000 events was collected of a relevant cell population after initial gating.
Gating strategy	Initial cell populations were gated for singlet and doublet cells using FSC-A/ FSC-W gating. A near-IR live/dead dye was used to discriminate between viable and dead cells. FMO control stained cells were used to distinguish between background staining and specific antibody staining. Detailed gating strategies were provided within the Supplementary Information.

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