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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	CosMx™ Spatial Molecular Imager data were generated using the Bruker Spatial CosMx SMI platform according to the manufacturer's instructions. Image acquisition and initial data processing (cell segmentation, transcript identification, and molecule-to-cell mapping) were performed using Bruker Spatial AtoMx™ Data Analysis Suite (v1.3.2). Visium Spatial Transcriptomics data were generated using the 10x Genomics Visium platform following the manufacturer's protocol. Raw sequencing data were processed with Space Ranger (v2.1.0) using the GRCh38 human reference genome to produce gene expression count matrices and spatial coordinates. No custom code was used for data collection. All subsequent analyses (described elsewhere) were performed using publicly available software packages in R (e.g., Seurat, CellChat).
Data analysis	All downstream analysis used a combination of commercial, open-source, and custom software, with code available at https://github.com/AmberBozward/SNH_AIH_spatial_transcriptome. CosMx data were segmented using AtoMx™ SIP (v1.0, Bruker) with Cellpose, then analyzed in R (v4.5.1) with Seurat (v5.1.0), Harmony (v3.8), SingleR (v2.1), DESeq2 (v1.48.1), and visualized using Searchlight (v2.0.3) with STRING (v11.5) and TRRUST (v2.0). Visium data were processed with Space Ranger (v2.1.0, 10x Genomics), analyzed in R (v4.5.1) with Seurat (v5.1.0), CombatSeq (SVA), DESeq2 (v1.48.1), and deconvoluted with CIBERSORTx; spatial neighborhood analysis was performed in Python (v3.10.18) using SquidPy (v1.6.5) and Scanpy (v1.11.13). Meta-transcriptomics reads were processed with fastp (v0.23.4), aligned with Bowtie2 (v2.5.4), quantified with Telescope (v1.0.3) and Salmon (v1.10.3), and differential expression visualized with EnhancedVolcano. Imaging data were analyzed with QuPath (v5.1), and confocal microscopy with Zen Black (v2.3) / Zen Lite (v3.12). Statistical analysis and figures used GraphPad Prism (v10) and RStudio (v2024.12.1+563). All custom scripts for spatial classification, pseudo-bulk generation, and reproducible workflows are available at the GitHub repository.

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

Our CosMx spatial transcriptomics data are freely available for user-friendly interactive browsing online (bham.ac.uk website in progress). All raw and processed sequencing data for Visium and meta-transcriptomics work are deposited in ArrayExpress under accession numbers E-MTAB-15851 and E-MTAB-15835 respectively. CosMx SMI raw and processed data is available on BioImage Archive accession number S-BIAD2346. Lists of genes used to identify cell subsets for analysis and clustering results are available as Supplementary Tables provided with this paper.

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	Human liver tissue samples were obtained from patients undergoing surgical procedures or liver transplantation. Sex was recorded in the clinical records of the patients as assigned at birth; gender identity was not systematically collected. The spatial transcriptomics data included 14 patients: 9 assigned female at birth and 5 assigned male at birth. Representative of autoimmune disease being female predominant. All patients provided written informed consent, including consent for use of de-identified tissue and data for research purposes. Sex was considered in study design where feasible, and analyses of immune and parenchymal cell populations were performed without stratification by sex due to limited sample numbers in each group. No sex- or gender-specific differential analyses were conducted, and findings are reported across the full cohort. The lack of sex- and gender-stratified analyses is justified by the small cohort size, which precludes robust statistical comparisons between sexes.
Reporting on race, ethnicity, or other socially relevant groupings	Ethnicity was collected from patient clinical records and categorized into two groups: Asian or Caucasian. These categories were used solely to describe the cohort and were not used as proxies for other variables such as socioeconomic status. Analyses were performed across the full cohort without stratification by ethnicity due to limited sample numbers in each group. Confounding variables related to ethnicity were not controlled. Individual-level de-identified ethnicity data are provided in the source data, and consent for data use was obtained from all participants.
Population characteristics	Human participants included patients undergoing liver surgery or transplantation, as well as donor livers surplus to clinical requirements. Covariate-relevant characteristics collected from clinical records included age, sex assigned at birth, body mass index (BMI), ethnicity (categorized as Asian or Caucasian), and liver function parameters including bilirubin, alanine aminotransferase (ALT), international normalized ratio (INR), and albumin. Disease groups included autoimmune hepatitis (AIH), seronegative liver disease (SN), and donors.
Recruitment	Participants were recruited from patients undergoing liver transplantation at the Queen Elizabeth Hospital, Birmingham, UK. Donor livers were included if rejected for transplantation. Recruitment was based on clinical availability, and no systematic self-selection or other biases are expected to have influenced the molecular or spatial analyses performed on the collected samples.
Ethics oversight	The study protocol was approved by the Local Research Ethics Committee at the University of Birmingham (REC reference 18/WA/0214, IRAS reference 223072). All participants provided written informed consent prior to sample collection.

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	Sample size was determined by available tissue for spatial transcriptomics and the number of samples that could be accommodated per spatial slide. Although no formal statistical calculation was performed, the chosen sample sizes provided sufficient biological and cellular representation within each disease group (autoimmune hepatitis, seronegative liver disease, and donors) for robust clustering, cell-type identification, and differential expression analyses.

Data exclusions	One sample was excluded from downstream analyses because it did not meet pre-established quality criteria (<50,000 reads). All other samples and cells passing quality control were included in the analyses.
Replication	Reproducibility of experimental findings was verified by analyzing multiple samples within each disease group (autoimmune hepatitis, seronegative liver disease, and donors) and by comparing results across two spatial transcriptomics platforms (CosMx and Visium). Key observations, including cell-type distributions, spatial patterns, and differential expression, were consistent across samples and platforms. All attempts at replication were successful.
Randomization	Samples were not randomly allocated into experimental groups. Group assignment was based on patients' clinical diagnosis (autoimmune hepatitis, seronegative liver disease) or donor status from rare human liver samples. Covariates such as age, sex, BMI, and liver function parameters were recorded and incorporated into downstream analyses where relevant. Randomisation was not applicable in this discovery study.
Blinding	Investigators were not blinded to group allocation during data collection or analysis. Blinding was not feasible because group assignment was determined by patient clinical diagnosis or donor status, which is inherently linked to the tissue samples. As analyses were primarily computational and objective (e.g., cell segmentation, clustering, and differential expression), no downstream sub-group analyses were performed, thus blinding was not required.

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	CD63 (NK1/C3, abcam, ab1318, 1044873-1), MMP12 (Polyclonal, abcam, ab137444, 1008991-2), SPP (Polyclonal, Protientech, 20416-AP, 00012666), ISG15 (Polyclonal, Protientech, 15981-1-AP, 00048190), OAS2 (Polyclonal, Protientech, 19279-1-AP, 00110190), MX1 (Polyclonal, Protientech, 13750-1-AP, 00177344), ASGR1 (Polyclonal, Protientech, 11739-1-AP, 00154572), CD68 (PG-M1, Invitrogen, MA5-12407, YF3963307), HERV (215/H4, amsbio, HERM-1811-5), LIGHT (Polyclonal, Invitrogen, PA5-104479, 2H43370), C1QA (1B10E3, Protientech, 67063-1-1g, 10008817), HVEM (Polyclonal, Protientech, 10138-1-AP, 00051250)
Validation	Primary antibodies were validated for use on human tissue and for the specific applications (immunohistochemistry or immunofluorescence) based on manufacturer datasheets, relevant literature citations, and antibody profiles in online databases such as The Human Protein Atlas. Where available, validation included staining patterns consistent with known tissue expression and expected subcellular localization.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*