

Spatial transcriptomics landscape of livers from patients with metabolic dysfunction-associated steatohepatitis

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Fig. S1. Distribution of individuals without metabolic dysfunction-associated steatohepatitis (NonMASH), those with MASH with low fibrosis (MASH-LF), and those with MASH with high fibrosis (MASH-HF) in *Vin^{en}* (A), *CD45^{en}* (B), and *Alb^{en}* (C) regions-of-interest (ROIs) from our GeoMx Digital Spatial Profiler (GeoMx DSP)-generated spatial transcriptomic dataset on principal component analysis plots.

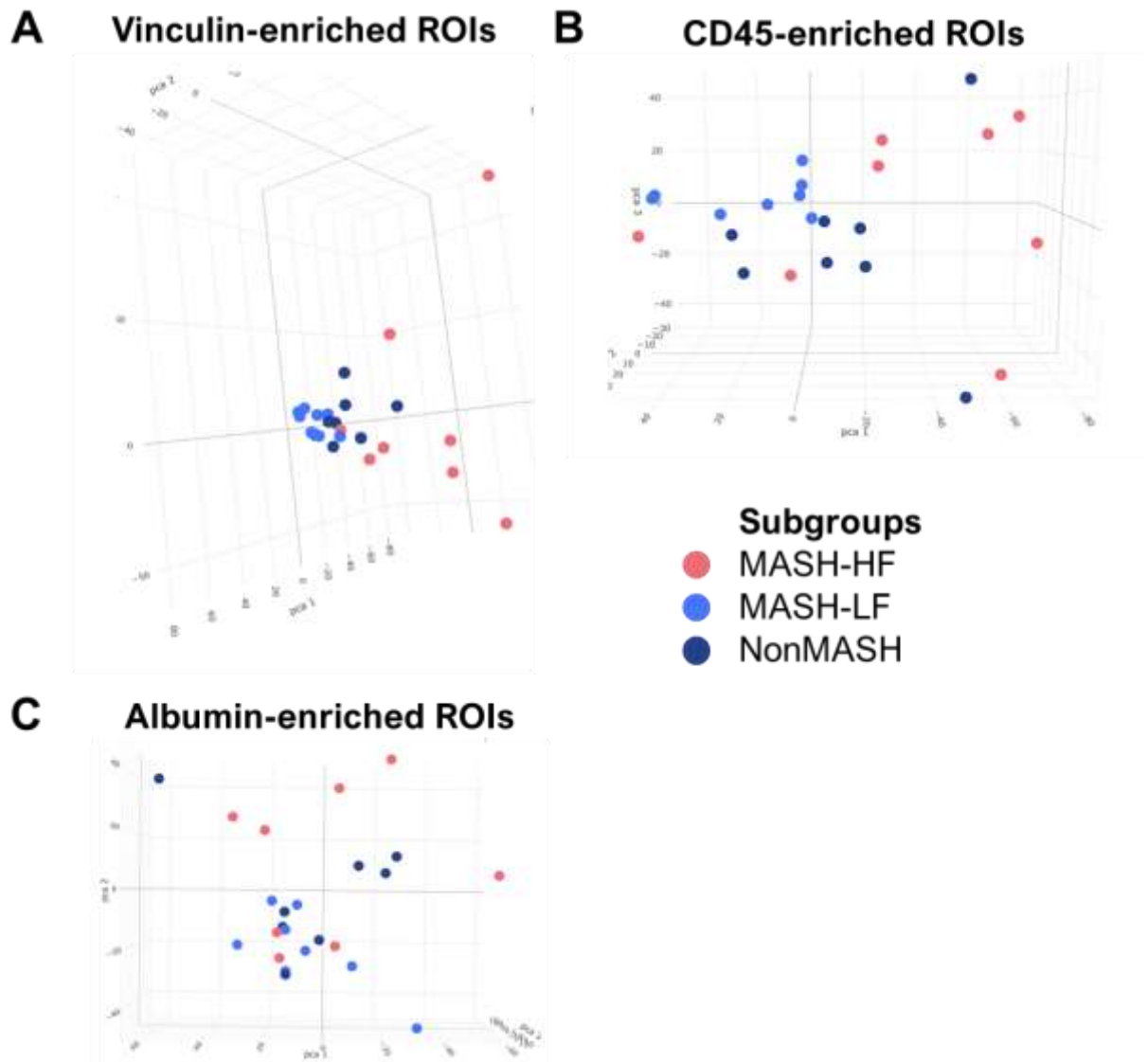


Fig. S2. Kyoto Encyclopedia of Genes and Genomes (KEGG) database-based gene set enrichment analysis (GSEA) results using differentially expressed genes (DEGs) (MASH vs. NonMASH); Top 40 pathways by normalized enrichment score (NES) in the *Vin^{en}* ROIs. * $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, and #False discovery rates (FDR) < 0.25 .**

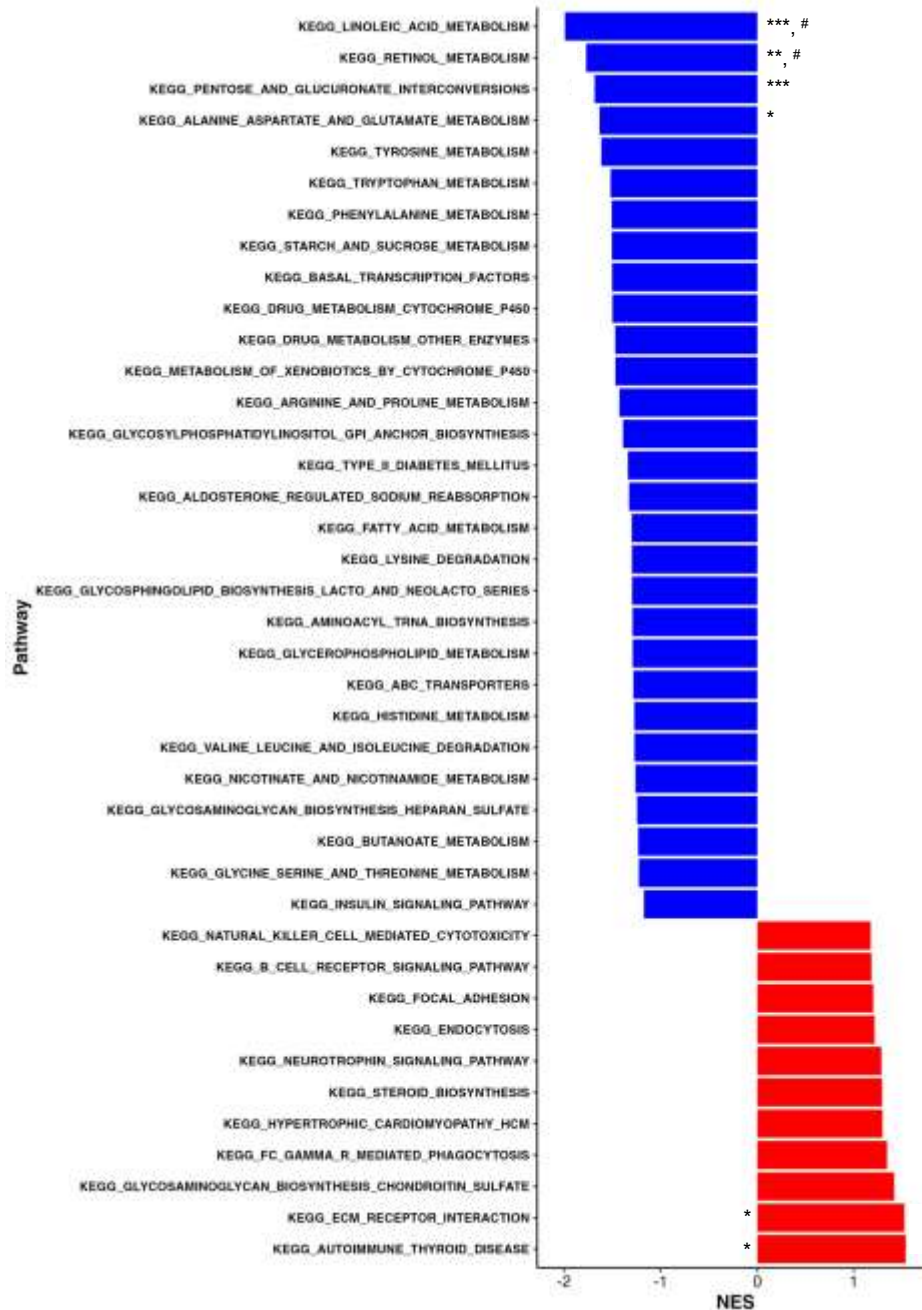


Fig. S3. KEGG database-based GSEA results using the DEGs (MASH vs. NonMASH); Top 40 pathways by NES in the CD45^{en} ROIs. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, and #FDR < 0.25.

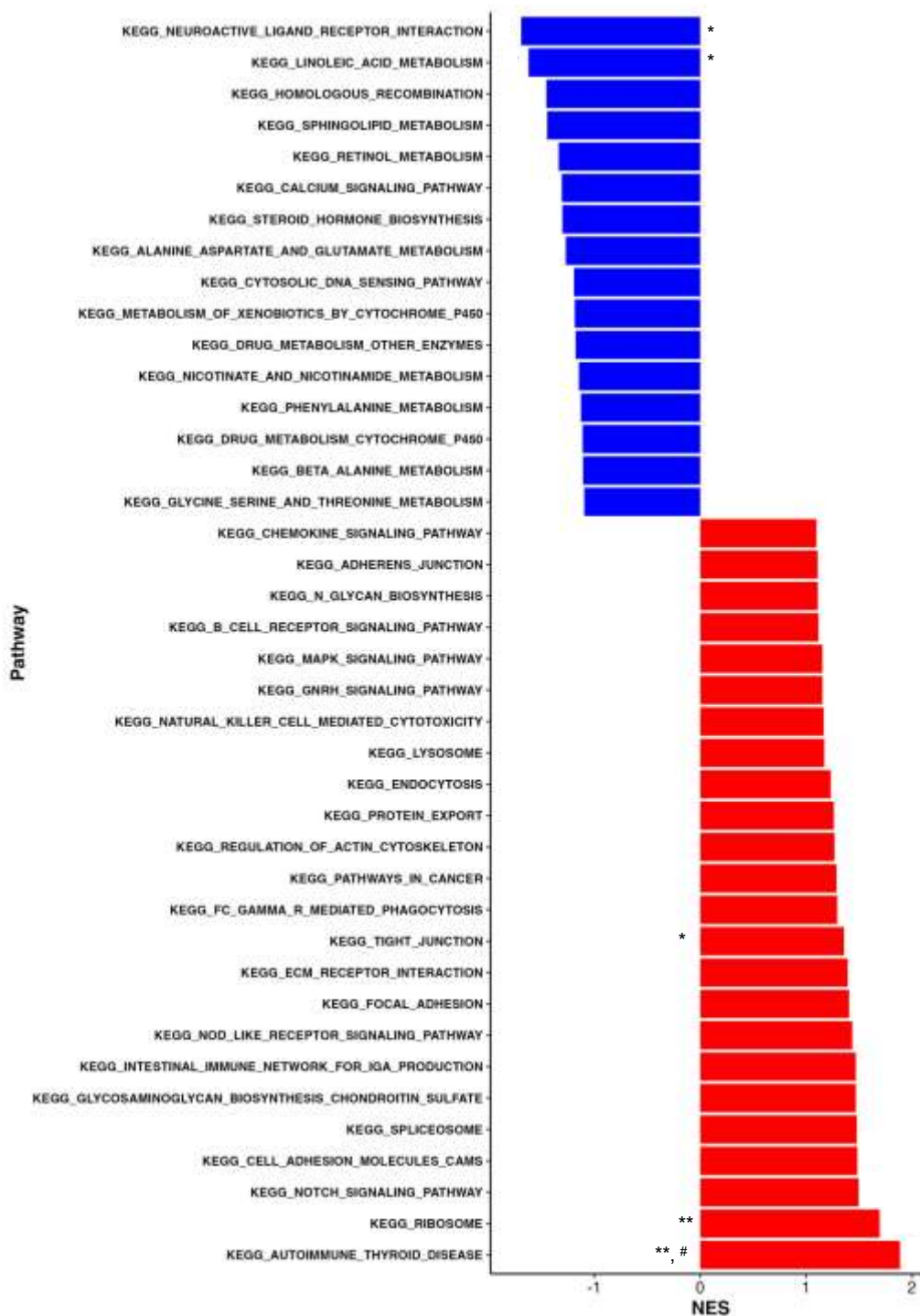


Fig. S4. KEGG database-based GSEA results using the DEGs (MASH vs. NonMASH); Top 40 pathways by NES in the Alb^{en} ROIs. * $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. No pathways met the FDR < 0.25.**

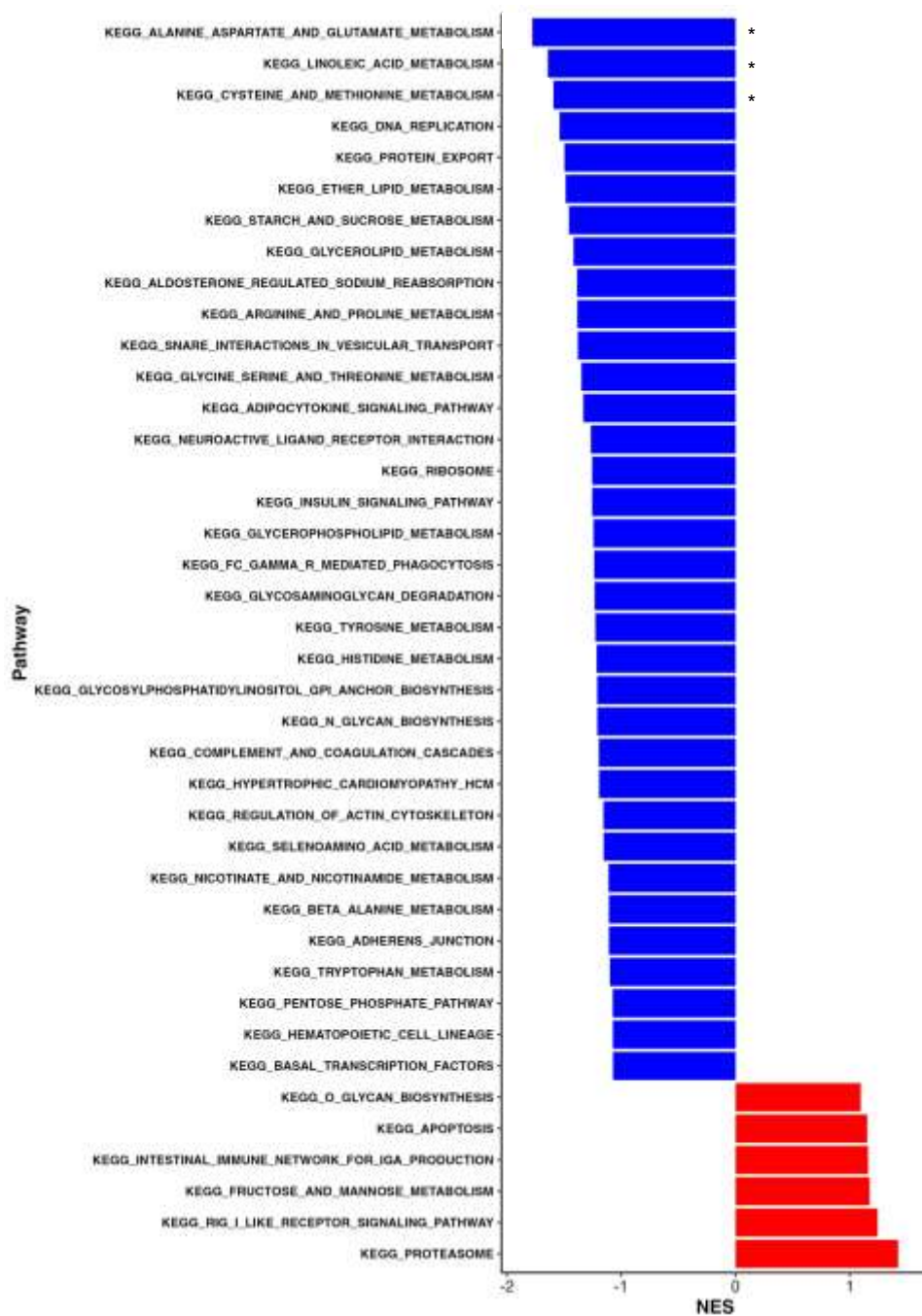


Fig. S5. Volcano plots showing DEGs (MASH vs. NonMASH) in the Vin^{en} (A), $CD45^{en}$ (B), and Alb^{en} (C). Genes with a blue outline indicate $FDR < 0.25$.

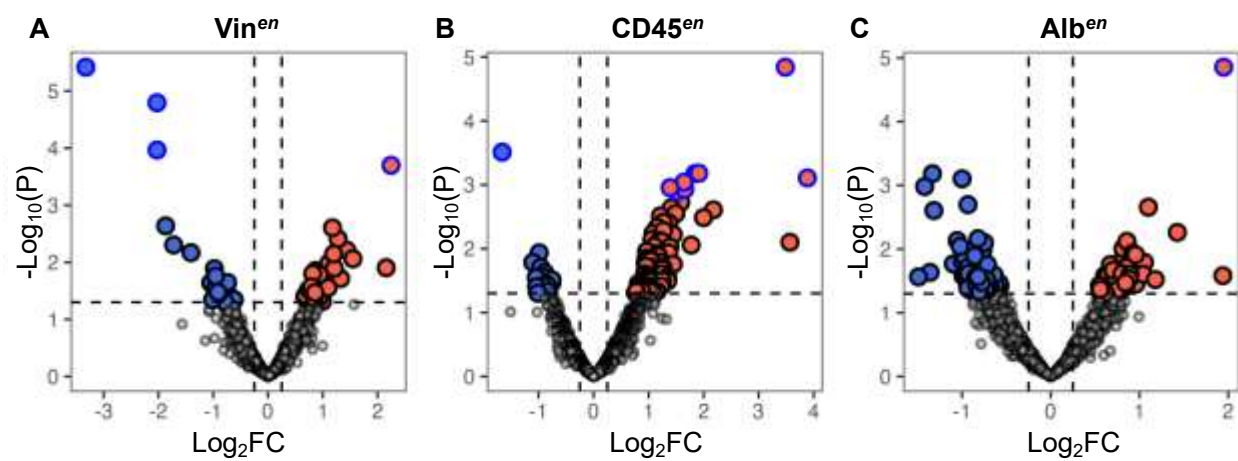


Fig. S6. Volcano plots showing DEGs (MASH-HF vs. MASH-LF) in the *Vin^{en}* (A), *CD45^{en}* (B), and *Alb^{en}* (C). Genes with a blue outline indicate FDR < 0.25.

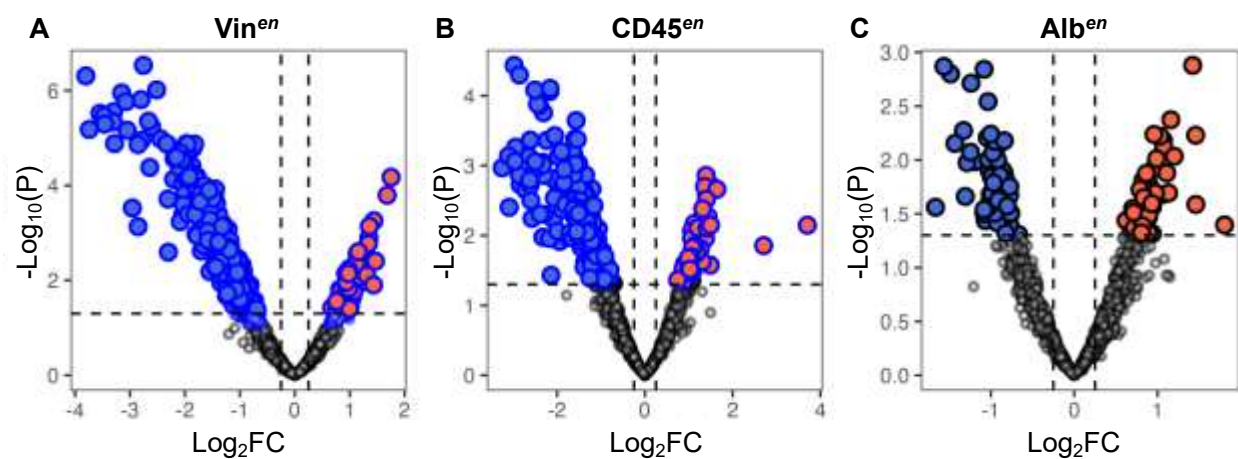


Fig. S7. Partial correlation analysis adjusted for age, sex, and body mass index (BMI), between clinical parameters and dysregulated genes in ROIs in MASH-HF versus MASH-LF. (A-C) Heatmaps showing partial correlation coefficients between clinical parameters and DEGs (MASH-HF versus MASH-LF) in (A) *Vin^{en}*, (B) *CD45^{en}*, and (C) *Alb^{en}* ROIs. Clinical parameters include histologic fibrosis stage, magnetic resonance elastography-liver stiffness measurement (MRE-LSM), enhanced liver fibrosis score (ELF score), plasma levels of cytokeratin 18 (CK-18) (U/L) and aldo-keto reductase family 1 member B10 (AKR1B10) (pg/mL). Red and blue colors indicate positive and negative correlations, respectively (partial correlation r from -1 to 1). Cells marked with # indicate statistically significant correlations (FDR < 0.25), while gray cells indicate non-significant correlations (FDR $\geq$ 0.25). Genes are grouped by pathway gene sets as indicated by the color bars on the left. AGE-RAGE, advanced glycation end products (AGE)-receptor for AGE (RAGE); KLF & SP, Krüppel-like factor and specificity protein; TGF- β , transforming growth factor-beta; HSC, hepatic stellate cell; ECM, extracellular matrix; HCC, hepatocellular carcinoma; PI3K-AKT, phosphatidylinositol 3-kinase-protein kinase B; TCA, tricarboxylic acid; JAK-STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; MASLD, metabolic dysfunction-associated steatotic liver diseases; VEGF, vascular endothelial growth factor; ER, endoplasmic reticulum; NAS, nonalcoholic fatty liver disease activity score.

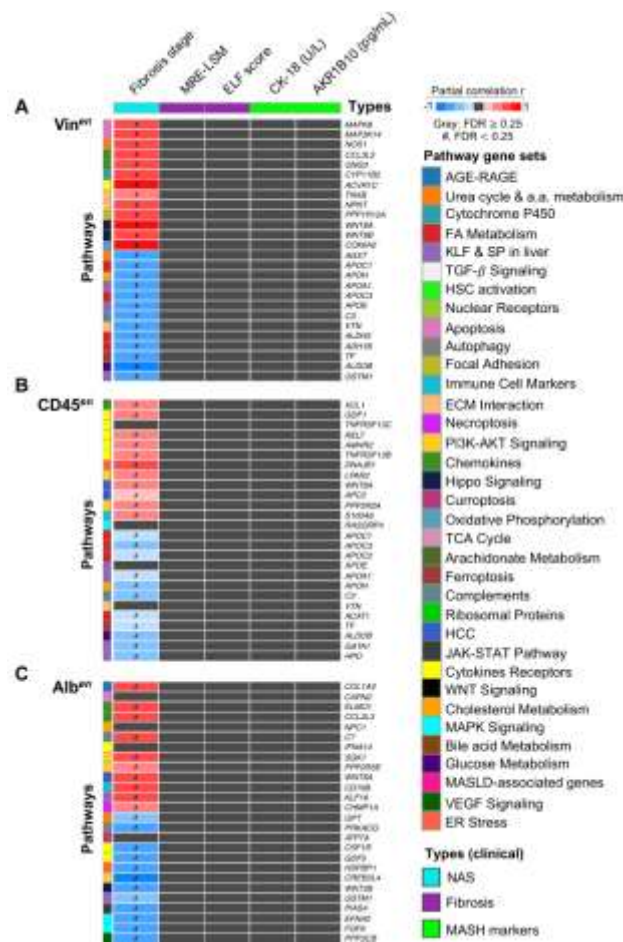
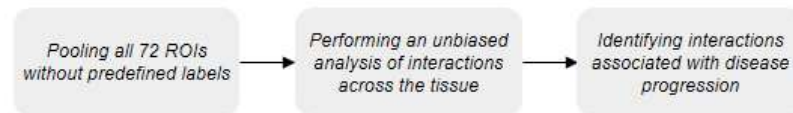


Fig. S8. Unbiased exploratory analysis of ligand-receptor interactions. (A) Workflow schematic. All 72 ROIs were first pooled under a single tissue-wide label and ligand-receptor interactions were identified across the whole tissue using CellPhoneDB. Interactions robustly detected across patients were retained and for each patient the three ROI segments were averaged into a single value to eliminate pseudoreplication of patient replicates. (B) Nine ligand-receptor interactions showing a significant association with MASH progression. The P-value above each panel is derived from Wilcoxon rank-sum test comparing each stage against the other two (one-vs-rest), reported as the smallest of the three comparisons for that interaction; asterisks denote pairwise significance between the two connected stages by Student's t-test. * $p < 0.05$; ** $p < 0.01$.

A



B

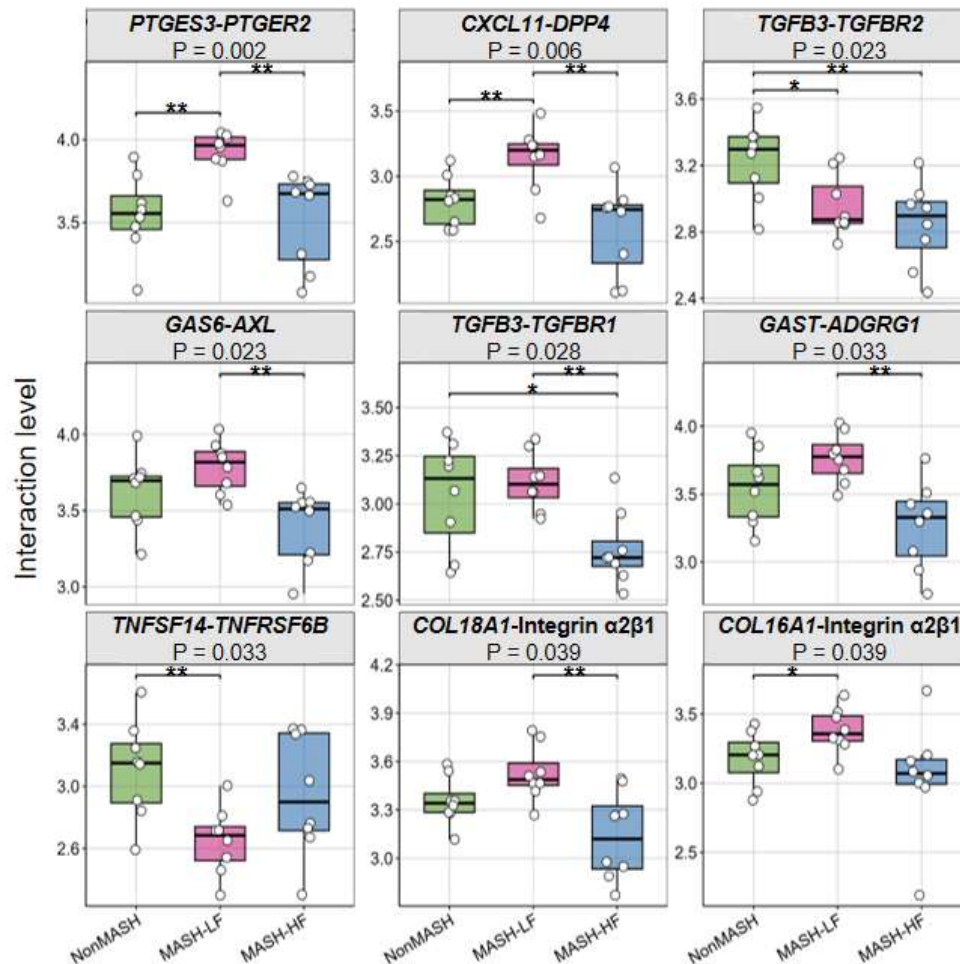


Fig. S9. Heatmaps of gene expression for the 78 genes of interest from the post- versus pre-bariatric surgery (BS) transcriptome dataset (GSE106737) and from our bulk RNA sequencing (RNA-Seq) dataset comparing MASH and NonMASH.

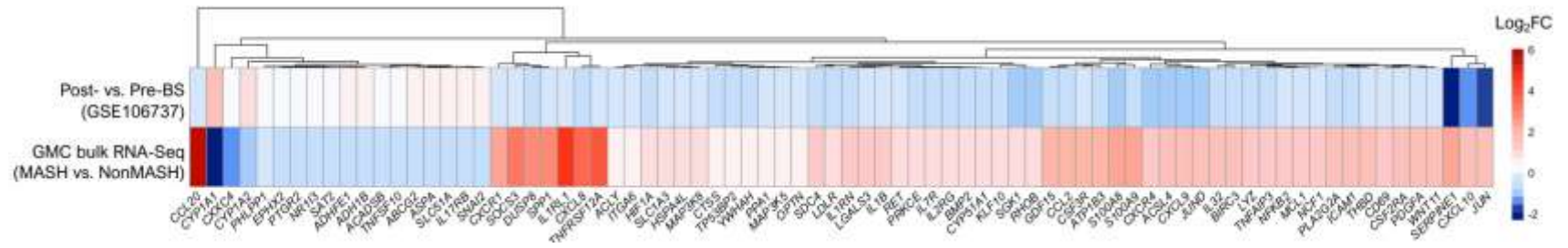


Fig. S10. Cytochrome P450 (CYP450) gene expression from *Vin^{en}* and *CD45^{en}* was highly correlated with their upstream transcription factors (TFs) and nuclear receptors (NRs). (A–B) We analyzed the correlation between CYP450 genes and TF-/NR-coding genes, which act as upstream regulators for CYP450 genes. Pearson's correlation coefficient was used to evaluate the associations between NR-encoding gene expression and *CYP1A2*, *CYP1A1*, and the 'CYP450 pathway score' (CYP450s), which reflects the overall transcriptional activity of the genes within CYP450 pathway genes. The correlations were visualized via Circos plots in *Vin^{en}* (A) and *CD45^{en}* (B), demonstrating the positive transcriptional regulation of CYP450 genes by TFs/NRs. The CYP450s was calculated via the GSVA package in R. (C–D) Circos plots displaying the correlation coefficients between CYP450s, *CYP1A2*, and *CYP1A1* with inflammatory cluster of differentiation (CD) antigens, with inflammatory genes labeled in green and anti-inflammatory genes labeled in brown.

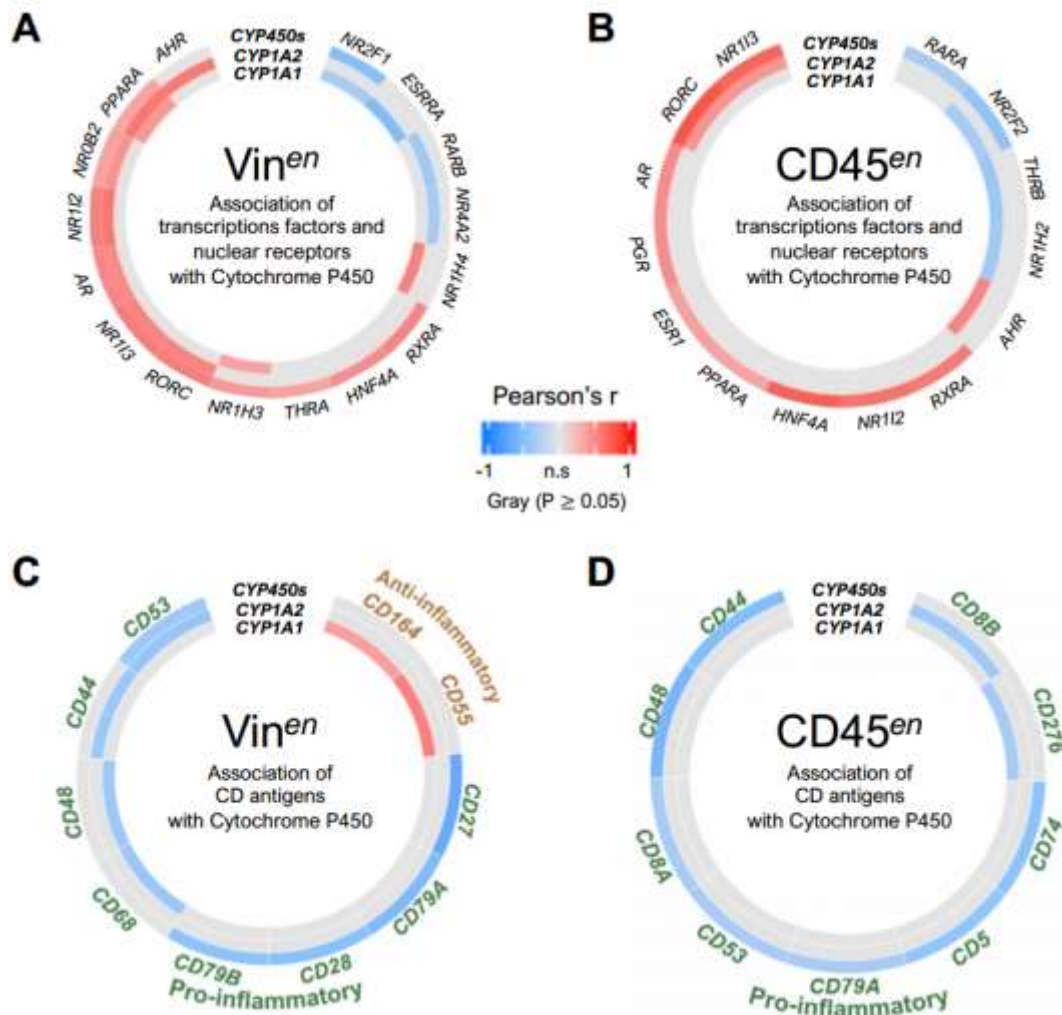


Fig. S11. Heatmaps of Pearson's correlations between TF-/NR-coding and CD antigen-coding genes in (A) *Vin^{en}* and (B) *CD45^{en}* ROIs. Pro-inflammatory CD genes are indicated as red.

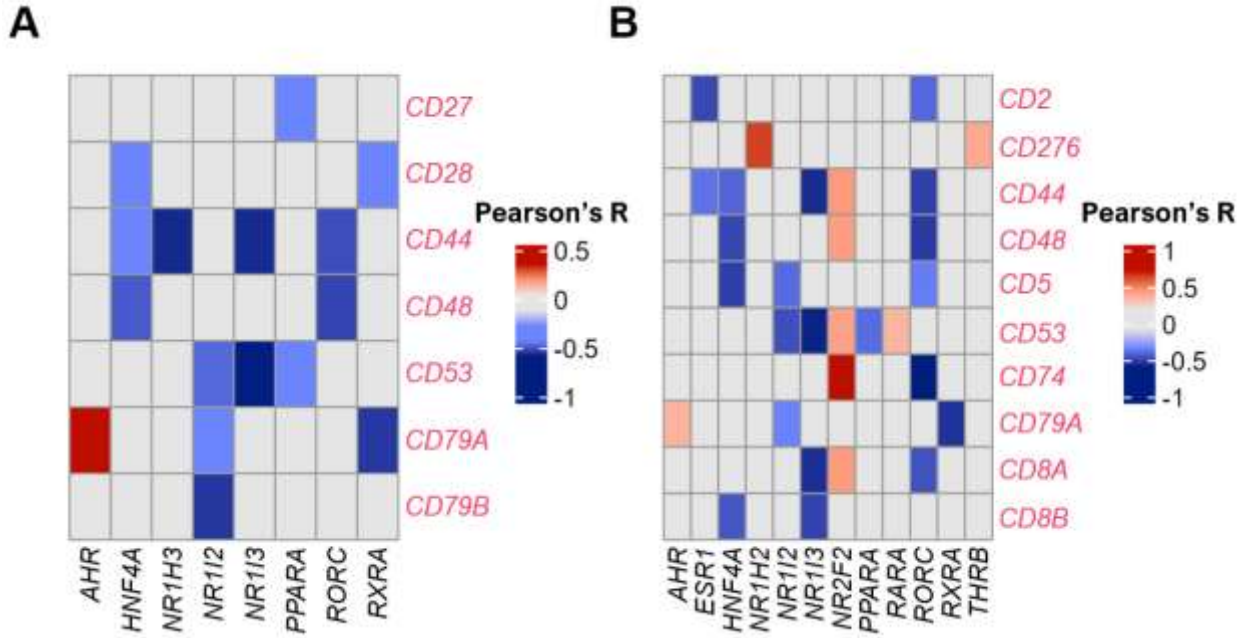


Fig. S12. Differential gene expression and its correlations with various clinical parameters in distinct ROIs. (A-C) Circos plots displaying the expression changes of genes in the *Vin^{en}* (A), *CD45^{en}* (B), and *Alb^{en}* (C) ROIs, as well as their correlation with MASH-related clinical parameters. The heatmap colors represent the log2 fold change (log2FC) of genes (MASH vs. NonMASH in the GeoMx DSP dataset) and partial correlation coefficients (r) with clinical parameters. Cells marked with # indicate statistically significant correlations (FDR < 0.25). LDL, low density lipoprotein; GGT, gamma-glutamyl transferase; HbA1c, glycosylated hemoglobin A1c; MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction.

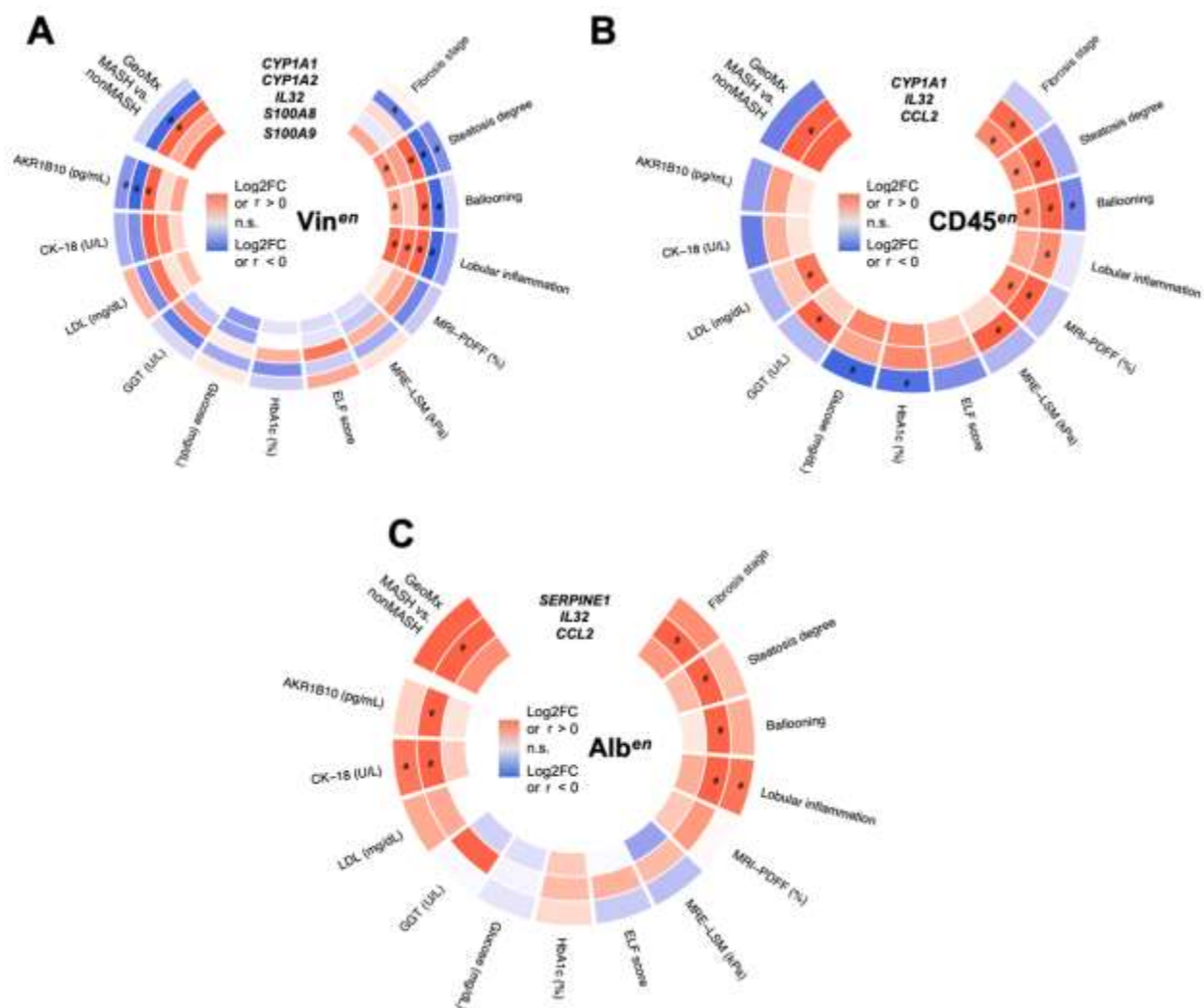


Fig. S13. A graphical abstract summarizing the study results across the three specific ROI types.

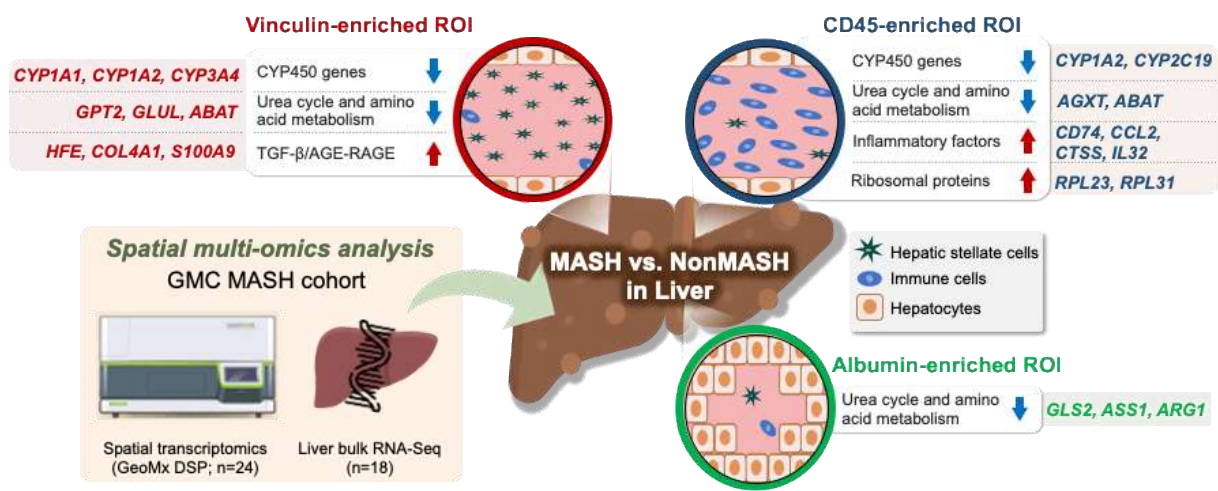


Table S1: Demographic and clinical characteristics of study subjects included in the bulk RNA-Seq analysis of liver tissues.

Characteristics	NonMASH (n = 8)	MASH (n = 10)	P values
Age (years)	32.0 (6.2)	35.6 (14.6)	0.493
Sex (male/female)	3/5	2/8	0.453
Weight (kg)	84.5 (16.4)	108.8 (29.3)	< 0.05
BMI (kg/m²)	30.5 (6.6)	40.1 (7.8)	< 0.05
WC (cm)	95.4 (12.6)	116.9 (18.4)	< 0.05
SBP (mmHg)	122.1 (16.1)	120.2 (10.8)	0.777
DBP (mmHg)	83.5 (9.4)	81.7 (10.2)	0.704
AST (U/L)	22.0 (5.9)	81.5 (50.9)	< 0.05
ALT (U/L)	27.8 (13.4)	128.1 (102.2)	< 0.05
GGT (U/L)	19.5 (9.5)	73.7 (47.4)	< 0.05
Total cholesterol (mg/dL)	182.1 (52.6)	202.4 (52.6)	0.429
HDL cholesterol (mg/dL)	48.4 (12.7)	45.5 (8.3)	0.591
Triglycerides (mg/dL)	124.8 (59.7)	216.1 (69.9)	< 0.05
HbA1c (%)	5.4 (0.3)	7.4 (1.9)	< 0.05
Glucose (mg/dL)	97.5 (24.1)	127.8 (55.7)	0.146

HOMA-IR2	1.5 (1.0)	3.6 (1.2)	< 0.05
FIB-4	0.4 (0.2)	1.1 (1.1)	0.113
ELF score	7.8 (0.3)	8.8 (1.2)	0.060
Liver MRI-PDFF (%)	10.7 (7.3)	23.5 (6.3)	< 0.05
MRE-LSM (kPa)	3.0 (0.5)	3.7 (1.3)	0.116
MRI-VAT area (cm²)	136.9 (41.7)	235.7 (93.6)	< 0.05
MRI-SAT area (cm²)	270.3 (109.8)	402.5 (121.6)	< 0.05

Data are expressed as the mean (standard deviation) or n (%), unless otherwise specified. WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin A1c; HOMA-IR2, homoeostatic model assessment 2 of insulin resistance; FIB-4, Fibrosis-4 index; ELF score, enhanced liver fibrosis score; MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction; MRE-LSM, magnetic resonance elastography-liver stiffness measurement; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table S2: Cell type-specific markers used to characterize hepatic cell populations. Cell type marker lists for hepatocytes, hepatic stellate cells, and immune cells from PanglaoDB, CellMarker (human), and manual curation.

Cell types	Cell markers
Hepatocytes	<i>APOA2 CYP2C9 A1CF ABCC3 ACADM AKR1C1 APOA5 CYP2D6 CYP7A1 ENTPD5 FGFR4 FGL1 FOSL1 FOXA3 GCK GPAT4 HMGCS1 LRP5 ORM1 PAH PLSCR1 PON3 RCAN1 RHOB SAA4 SAT2 SCD SEC16B SLBP SLC10A1 TKFC TP53INP2 TTC36 WTAP TF TTR APOE GATA4 ALB SERPINA1 CPS1 CYP3A4 HNF4A FGB</i>
Hepatic stellate cells	<i>ABCA8 CALD1 CLMN DPT EFHD1 EMP3 FOXS1 GPC6 HCFC1R1 LGALS1 MAP3K7CL MDK MYH11 NDUFA4L2 NTRK2 NTRK3 PARK7 PCOLCE PDGFA PHPT1 PPP1R12B RGS5 ZFPM2 OAF NOX4 EFEMP1 PAMR1 CKAP4 MMP14 COL8A1 EN1 PRRX1 NGF LAMC1 GJB2 TPM2 FOXF1 LRAT</i>
Immune cells	<i>CD79A HMGB2 HMGB1 NKG7 GZMB GZMH ZEB2 RUNX3 SLC2A1 CHST12 LLGL2 GSTP1 CEP78 ARL5A AHNAK HLA-DPA1 CLEC10A IL7R CD34 MGAT5 STRN3 MFN1 DCLRE1C C11orf96 ARGLU1 FFAR4 FABP5 CXCL9 CCL19 CCL21 CD274 ZFP36L2 ITGAM MPO IGKC TNFRSF13B MZB1 CD79B HLA-DMA CEACAM1 CD59 TOXCCR1 FBLN7 SGPP1 SLA ATP6V0A1 WHRN VPS54 TSPAN13 SOX4 SMS SMPD3 SLC35F2 SDC4 RNF187 PKM PAK2 OTUD5 NDUFA13 MYO5C MAN1A2 LDLRAD4 LAPTM4B HDAC7 GK EBI3 DYNLRB1 DYNLL1 DDIT4 COMMD3 CDKN1A CBX5 CASP1 CACYBP ATP1B1 ARPC1A STAT4 SLC4A10 ABCB1 PVRIG PARP8 TNFRSF13C POU2AF1 PDCCD1 MSH5 IGHG4 IGHG3 IGHG1 HMGA1 FKBP11 CD5 B3GAT1 PTPRCAP GNG7 BLK XCR1 SLAMF8 SIRPA PPL PLBD1 NR4A3 GPR132 ETV6 CLEC9A CAMK2D ASS1 TYMS CD247 BIRC5 OSM CHIT1 MAF GPR34 CPM LYN ITGB2 NCR3 HMBOX1 DUSP2 DOCK2 CD3G TRBC1 NABP1 JUNB CCL4L2 BCL6 IL10 SP100 IKZF1 ARHGEF1 ARHGAP45 ITGB8</i>

Table S3: MASH-associated pathway gene sets. Genes were selected to represent key biological pathways dysregulated in MASH and fibrosis based on the KEGG database and literature.

Pathway gene sets	Vin ^{en} ROI	CD45 ^{en} ROI	Alb ^{en} ROI	Genes
F01: Urea cycle-related amino acid metabolism (1) (KEGG accession: hsa00220; hsa00250)	included	included	included	ABAT ACY1 ACY3 ADSL ADSS1 ADSS2 AGXT AGXT2 ALDH4A1 ALDH5A1 ARG1 ARG2 ASL ASNS ASPA ASS1 CAD CPS1 DDO GAD1 GAD2 GFPT1 GFPT2 GLS GLS2 GLUD1 GLUD2 GLUL GOT1 GOT1L1 GOT2 GPT GPT2 IL4I1 NAGS NIT2 NOS1 NOS2 NOS3 OTC PPAT
F02: Cytochrome P450 (CYP450) (2)	included	included	included	CYP11B1 CYP11B2 CYP17A1 CYP1A1 CYP1A2 CYP26A1 CYP26B1 CYP27A1 CYP27B1 CYP27C1 CYP2A6 CYP2A7 CYP2B6 CYP2C18 CYP2C19 CYP2C8 CYP2C9 CYP2D6 CYP2D7 CYP2E1 CYP2F1 CYP2J2 CYP2R1 CYP2S1 CYP2U1 CYP2W1 CYP39A1 CYP3A4 CYP3A43 CYP3A5 CYP4A22 CYP4B1 CYP4F11 CYP4F12 CYP4F2 CYP4F22 CYP4F3 CYP4V2 CYP4X1 CYP4Z1 CYP51A1 CYP7A1 CYP8B1
F03: KLF & SP in liver (3, 4)	included	included	included	ABCA1 ABCG1 ACACA ACADM AGPAT1 AHR APOA1 APOE CD36 CETP CIDEA CPT1A CYP1A1 CYP1A2 CYP2B10 CYP2D6 CYP3A4 CYP4A10 CYP7A1 DGAT1 FASN FGF15 GCK GLI1 GLI2 GPAT1 GPBAR1 GPT GSTA1 GSTA2 GSTK1 GSTM1 GSTM2 GSTM3 GSTM4 GSTO1 GSTO2 GSTP1 GSTT1 HNF4A HPD KLF10 KLF11 KLF13 KLF14 KLF15 KLF16 KLF2 KLF3 KLF4 KLF5 KLF6 KLF7 KLF8 KLF9 LCAT LDLR MLXIPL MMP9 NAGS NR1H4 OCT4 PCK1 PCK2 PCNA PLIN1 PLIN2 PPARA PPARGC1A PRODH PTPN6 SCARB1 SERPINE1 SMAD2 SMAD3 SMAD4 SOX2 SP1 SP3 SREBF1 SULT1A1 SULT2B1 TDO2 TNFA TRIB3 UGT1A10 UGT1A8
F04: TGF- β signaling (1) (accession: hsa04350)	included	included	included	ACVR1 ACVR1B ACVR1C ACVR2A ACVR2B AMH AMHR2 BAMBI BMP2 BMP4 BMP5 BMP6 BMP7 BMP8A BMP8B BMPR1A BMPR1B BMPR2 CDKN2B CHRD CREBBP CUL1 DCN E2F4 E2F5 EMP3 EP300 FBN1 FMOD FST GDF5 GDF6 GDF7 GREM1 GREM2 HAMP HDAC1 HDAC2 HFE HJV ID1 ID2 ID3 ID4 IFNG IGSF1 INHBA INHBB INHBC INHBE LEFTY1 LEFTY2 LRRC32 LTBP1 MAPK1 MAPK3 MICOS10-NBL1 MYC NBL1 NCOR1 NEO1 NODAL NOG NRROS PITX2 PPP2CA PPP2CB PPP2R1A PPP2R1B RBL1 RBX1 RGMA RGMB RHOA ROCK1 RPS6KB1 RPS6KB2 SIN3A SKI SKIL SKP1 SMAD1 SMAD2 SMAD3 SMAD4 SMAD5 SMAD6 SMAD7 SMAD9 SMURF1 SMURF2

				SP1 TF TFDPI TFR2 TFRC TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 TGIF1 TGIF2 THBS1 THSD4 TNF ZFYVE16 ZFYVE9
F05: AGE- RAGE (1) (accession: hsa04933)	included	included	included	AGER AGT AGTR1 AKT1 AKT2 AKT3 BAX BCL2 CASP3 CCL2 CCND1 CDC42 CDK4 CDKN1B COL1A1 COL1A2 COL3A1 COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6 CXCL8 CYBB DIAPH1 EDN1 EGR1 F3 FN1 FOXO1 HRAS ICAM1 IL1A IL1B IL6 JAK2 JUN KRAS MAPK1 MAPK10 MAPK11 MAPK12 MAPK13 MAPK14 MAPK3 MAPK8 MAPK9 MMP2 NFATC1 NFKB1 NOS3 NOX1 NOX4 NRAS PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PIM1 PLCB1 PLCB2 PLCB3 PLCB4 PLCD1 PLCD3 PLCD4 PLCE1 PLCG1 PLCG2 PRKCA PRKCB PRKCD PRKCE PRKCZRAC1 RELA S100A8 S100A9 SELE SERPINE1 SMAD2 SMAD3 SMAD4 STAT1 STAT3 STAT5A STAT5B TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 THBD TNF VCAM1 VEGFA VEGFB VEGFC VEGFD
F06: HSC activation (5-8)	included	excluded	excluded	ACTA2 ADIPOQ ADIPOR1 ADIPOR2 CCL2 CCL5 COL1A1 COL1A2 COL3A1 CXCL10 GDF15 IL1B LEP LGALS3 SPARC TAGLN TGFB1 TNF TWIST1
F07: Cytokines- receptors (1) (accession: hsa04060)	included	included	included	ACKR3 ACKR4 ACVR1 ACVR1B ACVR1C ACVR2A ACVR2B ACVRL1 AMH AMHR2 BMP10 BMP15 BMP2 BMP3 BMP4 BMP5 BMP6 BMP7 BMP8A BMP8B BMPR1A BMPR1B BMPR2 CCL1 CCL11 CCL13 CCL14 CCL15 CCL16 CCL17 CCL18 CCL19 CCL2 CCL20 CCL21 CCL22 CCL23 CCL24 CCL25 CCL26 CCL27 CCL28 CCL3 CCL3L1 CCL3L3 CCL4 CCL4L1 CCL4L2 CCL5 CCL7 CCL8 CCR1 CCR10 CCR2 CCR3 CCR4 CCR5 CCR6 CCR7 CCR8 CCR9 CD27 CD4 CD40 CD40LG CD70 CLCF1 CNTF CNTFR CRLF2 CSF1 CSF1R CSF2 CSF2RA CSF2RB CSF3 CSF3R CSH1 CSH2 CTF1 CX3CL1 CX3CR1 CXCL1 CXCL10 CXCL11 CXCL12 CXCL13 CXCL14 CXCL16 CXCL17 CXCL2 CXCL3 CXCL5 CXCL6 CXCL8 CXCL9 CXCR1 CXCR2 CXCR3 CXCR4 CXCR5 CXCR6 EBI3 EDA EDA2R EDAR EPO EPOR FAS FASLG GDF1 GDF10 GDF11 GDF15 GDF2 GDF3 GDF5 GDF6 GDF7 GDF9 GH1 GH2 GHR IFNA1 IFNA10 IFNA13 IFNA14 IFNA16 IFNA17 IFNA2 IFNA21 IFNA4 IFNA5 IFNA6 IFNA7 IFNA8 IFNAR1 IFNAR2 IFNB1 IFNE IFNG IFNGR1 IFNGR2 IFNK IFNL1 IFNL2 IFNL3 IFNLR1 IFNW1 IL10 IL10RA IL10RB IL11 IL11RA IL12A IL12B IL12RB1 IL12RB2 IL13 IL13RA1 IL13RA2 IL15 IL15RA IL16 IL17A IL17B IL17C IL17D IL17F IL17RA IL17RB IL17RC IL17RE IL18 IL18R1 IL18RAP IL19 IL1A IL1B IL1F10 IL1R1 IL1R2 IL1RAP IL1RL1 IL1RL2 IL1RN IL2 IL20 IL20RA IL20RB IL21 IL21R IL22 IL22RA1 IL23A IL23R IL24 IL25 IL26 IL27 IL27RA IL2RA IL2RB IL2RG IL3 IL31 IL31RA IL32 IL33 IL34 IL36A IL36B IL36G IL36RN IL37 IL3RA IL4 IL4R IL5

				<i>IL5RA IL6 IL6R IL6ST IL7 IL7R IL9 IL9R INHA INHBA INHBB INHBC INHBE LEP LEPR LIF LIFR LTA LTB LTBR MPL MSTN NGF NGFR NODAL OSM OSMR PF4 PF4V1 PPBP PRL PRLR RELL1 RELL2 RELT TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 THPO TNF TNFRSF10A TNFRSF10B TNFRSF10C TNFRSF10D TNFRSF11A TNFRSF11B TNFRSF12A TNFRSF13B TNFRSF13C TNFRSF14 TNFRSF17 TNFRSF18 TNFRSF19 TNFRSF1A TNFRSF1B TNFRSF21 TNFRSF25 TNFRSF4 TNFRSF6B TNFRSF8 TNFRSF9 TNFSF10 TNFSF11 TNFSF12 TNFSF13 TNFSF13B TNFSF14 TNFSF15 TNFSF18 TNFSF4 TNFSF8 TNFSF9 TSLP XCL1 XCL2 XCR1</i>
F08: Immune cell markers (8)	excluded	included	excluded	<i>CD163 CD2 CD20 CD247 CD37 CD38 CD3D CD5L CD68 CD69 CD7 CD74 CD79A CD79B CPVL GZMK IGHG1 IGKC IL18 KLRB1 KLRD1 LGLC2 LTB LYZ MARCO MKI67 NCAM1 NKG2A NKG7 S100A6 S100A8 S100A9 STMN1 TRAC TRDC VCAM1 VCAN VSIG4</i>
F09: Arachidonate metabolism (1) (accession: hsa00590)	included	included	excluded	<i>AKR1C3 ALOX12 ALOX12B ALOX15 ALOX15B ALOX5 ALOXE3 CBR1 CBR3 CYP2B6 CYP2C19 CYP2C8 CYP2C9 CYP2E1 CYP2J2 CYP2U1 CYP4F2 CYP4F3 CYP4F8 EPHX2 GGT1 GGT5 GPX4 HPGD HPGDS JMJD7- PLA2G4B LTA4H LTC4S PLA2G10 PLA2G12A PLA2G12B PLA2G1B PLA2G2A PLA2G2C PLA2G2D PLA2G2E PLA2G2F PLA2G3 PLA2G4A PLA2G4B PLA2G4C PLA2G4D PLA2G4E PLA2G4F PLA2G5 PLA2G6 PLAAT2 PLAAT3 PLB1 PRXL2B PTGDS PTGES PTGES2 PTGES3 PTGIS PTGR1 PTGR2 PTGR3 PTGS1 PTGS2 TBXAS1</i>
F10: Ribosomal proteins (1) (accession: hsa03010)	included	included	included	<i>RPL10 RPL10A RPL10L RPL11 RPL12 RPL13 RPL13A RPL14 RPL15 RPL17 RPL18 RPL18A RPL19 RPL21 RPL22 RPL22L1 RPL23 RPL23A RPL24 RPL26 RPL26L1 RPL27 RPL27A RPL28 RPL29 RPL3 RPL30 RPL31 RPL32 RPL34 RPL35 RPL35A RPL36 RPL36A RPL36AL RPL37 RPL37A RPL38 RPL39 RPL3L RPL4 RPL41 RPL5 RPL6 RPL7 RPL7A RPL8 RPL9 RPLP0 RPLP1 RPLP2 RPS10 RPS11 RPS12 RPS13 RPS14 RPS15 RPS15A RPS16 RPS17 RPS18 RPS19 RPS2 RPS20 RPS21 RPS23 RPS24 RPS25 RPS26 RPS27 RPS27A RPS27L RPS28 RPS29 RPS3 RPS3A RPS4X RPS4Y1 RPS4Y2 RPS5 RPS6 RPS7 RPS8 RPS9 RPSA</i>
F11: Autophagy (1) (accession: hsa04140)	included	included	included	<i>AKT1 AKT1S1 AKT2 AKT3 AMBRA1 ATG10 ATG101 ATG12 ATG13 ATG14 ATG16L1 ATG16L2 ATG2A ATG2B ATG3 ATG4A ATG4B ATG4C ATG4D ATG5 ATG7 ATG9A ATG9B BAD BCL2 BCL2L1 BECN1 BECN2 BIRC6 BNIP3 C9orf72 CALCOCO2 CAMKK2 CFLAR CTSD CTSL DAPK1 DAPK2 DAPK3 DDIT4 DEPTOR EIF2AK3 EIF2AK4 EIF2S1 EPG5 ERN1 GABARAP GABARAPL1 GABARAPL2</i>

				GORASP1 GORASP2 HIF1A HMGB1 HRAS IGBP1 IGF1R INS IRS1 IRS2 IRS4 ITPR1 KRAS LAMP1 LAMP2 MAP1LC3A MAP1LC3B MAP1LC3B2 MAP1LC3C MAP2K1 MAP2K2 MAP3K7 MAPK1 MAPK10 MAPK3 MAPK8 MAPK9 MLST8 MRAS MTMR14 MTMR3 MTMR4 MTOR NBR1 NRAS NRBF2 OPTN PDPK1 PIK3C3 PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PIK3R4 PLEKHM1 PPP2CA PPP2CB PRAP1 PRKAA1 PRKAA2 PRKACA PRKACB PRKACG PRKCD PRKCQ PTEN RAB1A RAB33B RAB39B RAB7A RAB7B RAB8A RAF1 RB1CC1 RHEB RPS27A RPS6KB1 RPS6KB2 RPTOR RRAGA RRAGB RRAGC RRAGD RRAS RRAS2 RUBCN SH3GLB1 SMCR8 SNAP29 SQSTM1 STK11 STX17 STX7 SUPT20H TANK TAX1BP1 TBK1 TP53INP2 TRAF6 TSC1 TSC2 UBA52 UBB UBC ULK1 ULK2 UVRAG VAMP8 VMP1 VPS11 VPS16 VPS18 VPS33A VPS39 VPS41 WDFY3 WDR41 WDR45 WDR45B WIPI1 WIPI2 YKT6 ZFYVE1
F12: Cholesterol metabolism (1, 9, 10) (accession: hsa04979)	included	included	included	ABCA1 ABCB11 ABCG5 ABCG8 ANGPTL3 ANGPTL4 ANGPTL8 APOA1 APOA2 APOA4 APOB APOC1 APOC2 APOC3 APOE APOH CD36 CETP CIDEA CYP27A1 CYP7A1 DGAT1 DGAT2 FOXA2 LCAT LDLR LDLRAP1 LIPA LIPCLIPG LPALPL LRP1 LRP2 LRPAP1 MTP MYLIP NCEH1 NPC1 NPC2 NR1H2 NR1H3 OSBPL5 PCSK9 PLTP SCARB1 SOAT1 SOAT2 SORT1 STAR STARD3 TM6SF2 TSPO VAPA VAPB VDAC1 VDAC2 VDAC3
F13: MAPK signaling (1) (accession: hsa04010)	included	included	included	AKT1 AKT2 AKT3 ANGPT1 ANGPT2 ANGPT4 ARAF AREG ARRB1 ARRB2 ARTN ATF2 ATF4 BDNF BRAF CACNA1A CACNA1B CACNA1C CACNA1D CACNA1E CACNA1F CACNA1G CACNA1H CACNA1I CACNA1S CACNA2D1 CACNA2D2 CACNA2D3 CACNA2D4 CACNB1 CACNB2 CACNB3 CACNB4 CACNG1 CACNG2 CACNG3 CACNG4 CACNG5 CACNG6 CACNG7 CACNG8 CASP3 CD14 CDC25B CDC42 CHUK CRK CRKL CSF1 CSF1R DAXX DDIT3 DUSP1 DUSP10 DUSP16 DUSP2 DUSP3 DUSP4 DUSP5 DUSP6 DUSP7 DUSP8 DUSP9 ECSIT EFNA1 EFNA2 EFNA3 EFNA4 EFNA5 EGF EGFR ELK1 ELK4 EPHA2 ERBB2 ERBB3 ERBB4 EREG FAS FASLG FGF1 FGF10 FGF16 FGF17 FGF18 FGF19 FGF2 FGF20 FGF21 FGF22 FGF23 FGF3 FGF4 FGF5 FGF6 FGF7 FGF8 FGF9 FGFR1 FGFR2 FGFR3 FGFR4 FLNA FLNB FLNC FLT1 FLT3 FLT3LG FLT4 FOS GADD45A GADD45B GADD45G GDNF GNA12 GNG12 GRB2 HGF HRAS HSPA1A HSPA1B HSPA1L HSPA6 HSPA8 HSPB1 IGF1 IGF1R IGF2 IKBKB IKBKG IL1A IL1B IL1R1 IL1RAP INS INSR IRAK1 IRAK4 JMJD7-PLA2G4B JUN JUND KDR KIT KITLG KRAS LAMTOR3 MAP2K1 MAP2K2 MAP2K3 MAP2K4 MAP2K5 MAP2K6 MAP2K7 MAP3K1 MAP3K10 MAP3K11 MAP3K12 MAP3K13 MAP3K14 MAP3K2 MAP3K20 MAP3K21

				MAP3K3 MAP3K4 MAP3K5 MAP3K6 MAP3K7 MAP3K8 MAP3K9 MAP4K1 MAP4K2 MAP4K3 MAP4K4 MAPK1 MAPK10 MAPK11 MAPK12 MAPK13 MAPK14 MAPK3 MAPK7 MAPK8 MAPK8IP1 MAPK8IP2 MAPK8IP3 MAPK9 MAPKAPK2 MAPKAPK3 MAPKAPK5 MAPT MAX MECOM MEF2C MET MKNK1 MKNK2 MRAS MYC MYD88 NF1 NFATC1 NFATC3 NFKB1 NFKB2 NGF NGFR NLK NR4A1 NRAS NRTN NTF3 NTF4 NTRK1 NTRK2 PAK1 PAK2 PDGFA PDGFB PDGFC PDGFD PDGFRA PDGFRB PGF PLA2G4A PLA2G4B PLA2G4C PLA2G4D PLA2G4E PLA2G4F PPM1A PPM1B PPP3CA PPP3CB PPP3CC PPP3R1 PPP3R2 PPP5C PRKACA PRKACB PRKACG PRKCA PRKCB PRKCG PSPN PTPN5 PTPN7 PTPRR RAC1 RAC2 RAC3 RAF1 RAP1A RAP1B RAPGEF2 RASA1 RASA2 RASGRF1 RASGRF2 RASGRP1 RASGRP2 RASGRP3 RASGRP4 RELA RELB RET RPS6KA1 RPS6KA2 RPS6KA3 RPS6KA4 RPS6KA5 RPS6KA6 RRAS RRAS2 SOS1 SOS2 SRF STK3 STK4 STMN1 TAB1 TAB2 TAOK1 TAOK2 TAOK3 TEK TGFA TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 TNF TNFRSF1A TP53 TRADD TRAF2 TRAF6 VEGFA VEGFB VEGFC VEGFD
F14: Ferroptosis (1) (accession: hsa04216)	included	included	included	ACSL1 ACSL3 ACSL4 ACSL5 ACSL6 ALOX15 ATG5 ATG7 CP CYBB FTH1 FTL FTMT GCLC GCLM GPX4 GSS HMOX1 LPCAT3 MAP1LC3A MAP1LC3B MAP1LC3B2 MAP1LC3C NCOA4 PCBP1 PCBP2 PRNP SAT1 SAT2 SLC11A2 SLC39A14 SLC39A8 SLC3A2 SLC40A1 SLC7A11 STEAP3 TF TFRC TP53 VDAC2 VDAC3
F15: GFR-PI3K-AKT pathway (1) (accession: hsa04151)	included	included	included	AKT1 AKT2 AKT3 ANGPT1 ANGPT2 ANGPT4 AREG ARTN ATF2 ATF4 ATF6B BAD BCL2 BCL2L1 BCL2L11 BDNF BRCA1 C8orf44-SGK3 CASP9 CCND1 CCND2 CCND3 CCNE1 CCNE2 CD19 CDC37 CDK2 CDK4 CDK6 CDKN1A CDKN1B CHAD CHRM1 CHRM2 CHUK COL1A1 COL1A2 COL2A1 COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6 COL6A1 COL6A2 COL6A3 COL6A5 COL6A6 COL9A1 COL9A2 COL9A3 COMP CREB1 CREB3 CREB3L1 CREB3L2 CREB3L3 CREB3L4 CREB5 CRTC2 CSF1 CSF1R CSF3 CSF3R CSH1 CSH2 DDIT4 EFNA1 EFNA2 EFNA3 EFNA4 EFNA5 EGF EGFR EIF4B EIF4E EIF4E1B EIF4E2 EIF4EBP1 EPHA2 EPO EPOR ERBB2 ERBB3 ERBB4 EREG F2R FASLG FGF1 FGF10 FGF16 FGF17 FGF18 FGF19 FGF2 FGF20 FGF21 FGF22 FGF23 FGF3 FGF4 FGF5 FGF6 FGF7 FGF8 FGF9 FGFR1 FGFR2 FGFR3 FGFR4 FLT1 FLT3 FLT3LG FLT4 FN1 FOXO3 G6PC1 G6PC2 G6PC3 GDNF GH1 GH2 GHR GNB1 GNB2 GNB3 GNB4 GNB5 GNG10 GNG11 GNG12 GNG13 GNG2 GNG3 GNG4 GNG5 GNG7 GNG8 GNGT1 GNGT2 GRB2 GSK3B GYS1 GYS2 HGF HRAS HSP90AA1 HSP90AB1 HSP90B1

				<i>IBSP IFNA1 IFNA10 IFNA13 IFNA14 IFNA16 IFNA17 IFNA2 IFNA21 IFNA4 IFNA5 IFNA6 IFNA7 IFNA8 IFNAR1 IFNAR2 IFNB1 IGF1 IGF1R IGF2 IGH IKBKB IKBKG IL2 IL2RA IL2RB IL2RG IL3 IL3RA IL4 IL4R IL6 IL6R IL7 IL7R INS INSR IRS1 ITGA1 ITGA10 ITGA11 ITGA2 ITGA2B ITGA3 ITGA4 ITGA5 ITGA6 ITGA7 ITGA8 ITGA9 ITGAV ITGB1 ITGB3 ITGB4 ITGB5 ITGB6 ITGB7 ITGB8 JAK1 JAK2 JAK3 KDR KIT KITLG KRAS LAMA1 LAMA2 LAMA3 LAMA4 LAMA5 LAMB1 LAMB2 LAMB3 LAMB4 LAMC1 LAMC2 LAMC3 LPAR1 LPAR2 LPAR3 LPAR4 LPAR5 LPAR6 MAGI1 MAGI2 MAP2K1 MAP2K2 MAPK1 MAPK3 MCL1 MDM2 MET MLST8 MTCP1 MTOR MYB MYC NFKB1 NGF NGFR NOS3 NR4A1 NRAS NRTN NTF3 NTF4 NTRK1 NTRK2 OSM OSMR PCK1 PCK2 PDGFA PDGFB PDGFC PDGFD PDGFRA PDGFRB PDPK1 PGF PHLPP1 PHLPP2 PIK3AP1 PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 PIK3R2 PIK3R3 PIK3R5 PIK3R6 PKN1 PKN2 PKN3 PPP2CA PPP2CB PPP2R1A PPP2R1B PPP2R2A PPP2R2B PPP2R2C PPP2R2D PPP2R3A PPP2R3B PPP2R3C PPP2R5A PPP2R5B PPP2R5C PPP2R5D PPP2R5E PRKAA1 PRKAA2 PRKCA PRL PRLR PSPN PTEN PTK2 RAC1 RAF1 RBL2 RELA RELN RET RHEB RPS6 RPS6KB1 RPS6KB2 RPTOR RXRA SGK1 SGK2 SGK3 SOS1 SOS2 SPP1 STK11 SYK TCL1A TCL1B TEK TGFA THBS1 THBS2 THBS3 THBS4 THEM4 TLR2 TLR4 TNC TNN TNR TNXB TP53 TSC1 TSC2 VEGFA VEGFB VEGFC VEGFD VTN VWF YWHAB YWHAE YWHAG YWHAH YWHAQ YWHAZ</i>
F16: Necroptosis (1) (accession: hsa04217)	included	included	included	<i>AIFM1 ALOX15 BAX BCL2 BID BIRC2 BIRC3 CAMK2A CAMK2B CAMK2D CAMK2G CAPN1 CAPN2 CASP1 CASP8 CFLAR CHMP1A CHMP1B CHMP2A CHMP2B CHMP3 CHMP4A CHMP4B CHMP4C CHMP5 CHMP6 CHMP7 CYBB CYLD DNM1L EIF2AK2 FADD FAS FASLG FTH1 FTL GLUD1 GLUD2 GLUL H2AB1 H2AB2 H2AB3 H2AC1 H2AC11 H2AC12 H2AC13 H2AC14 H2AC15 H2AC16 H2AC17 H2AC18 H2AC19 H2AC20 H2AC21 H2AC25 H2AC4 H2AC6 H2AC7 H2AC8 H2AJ H2AL3 H2AX H2AZ1 H2AZ2 HMGB1 HSP90AA1 HSP90AB1 IFNA1 IFNA10 IFNA13 IFNA14 IFNA16 IFNA17 IFNA2 IFNA21 IFNA4 IFNA5 IFNA6 IFNA7 IFNA8 IFNAR1 IFNAR2 IFNB1 IFNG IFNGR1 IFNGR2 IL1A IL1B IL33 IRF9 JAK1 JAK2 JAK3 JMJD7-PLA2G4B MACROH2A1 MACROH2A2 MAPK10 MAPK8 MAPK9 MLKL NLRP3 PARP1 PGAM5 PLA2G4A PLA2G4B PLA2G4C PLA2G4D PLA2G4E PLA2G4F PPIA PPID PYCARD PYGB PYGL PYGM RBCK1 RIPK1 RIPK3 RNF103-CHMP3 RNF31 SHARPIN SLC25A31 SLC25A4 SLC25A5 SLC25A6 SMPD1 SPATA2 SPATA2L SQSTM1 STAT1 STAT2 STAT3 STAT4 STAT5A STAT5B STAT6 TICAM1 TICAM2 TLR3 TLR4 TNF TNFAIP3 TNFRSF10A TNFRSF10B TNFRSF1A TNFSF10 TRADD</i>

				TRAF2 TRAF5 TRPM7 TYK2 USP21 VDAC1 VDAC2 VDAC3 VPS4A VPS4B XIAP ZBP1
F17: Nuclear receptor-related (9, 11, 12)	included	included	included	ACADM ACADS ACADVL ADIPOQ CD36 CDK5 CDK7 CDK9 CEBPA FABP4 FGF1 FGF21 GK GLUT4 IRS1 IRS2 LPL LXRA LXR B NR1H4 NR1I2 NR1I3 PEPCK PI3KCA PPARA PPARB PPARG PPARGC1A PPARGC1B RXR SIRT1 SORBS1 STAT1 STAT5A STAT5B TNF
F18: Oxidative phosphorylation (1, 9) (accession: hsa00190)	included	included	included	ATP12A ATP4A ATP4B ATP5F1A ATP5F1B ATP5F1C ATP5F1D ATP5F1E ATP5MC1 ATP5MC2 ATP5MC3 ATP5ME ATP5MF ATP5MG ATP5PB ATP5PD ATP5PF ATP5PO ATP6 ATP6AP1 ATP6V0A1 ATP6V0A2 ATP6V0A4 ATP6V0B ATP6V0C ATP6V0D1 ATP6V0D2 ATP6V0E1 ATP6V0E2 ATP6V1A ATP6V1B1 ATP6V1B2 ATP6V1C1 ATP6V1C2 ATP6V1D ATP6V1E1 ATP6V1E2 ATP6V1F ATP6V1G1 ATP6V1G2 ATP6V1G3 ATP6V1H ATP8 COX1 COX10 COX11 COX15 COX17 COX2 COX3 COX4 COX4I1 COX4I2 COX5A COX5B COX6A1 COX6A2 COX6B1 COX6B2 COX6C COX7A1 COX7A2 COX7A2L COX7B COX7B2 COX7C COX8A COX8C CYC1 CYCS CYTB ESRRALHPP ND1 ND2 ND3 ND4 ND4L ND5 ND6 NDUFA1 NDUFA10 NDUFA11 NDUFA12 NDUFA13 NDUFA2 NDUFA3 NDUFA4 NDUFA4L2 NDUFA5 NDUFA6 NDUFA7 NDUFA8 NDUFA9 NDUFAB1 NDUFB1 NDUFB10 NDUFB11 NDUFB2 NDUFB3 NDUFB4 NDUFB5 NDUFB6 NDUFB7 NDUFB8 NDUFB9 NDUFC1 NDUFC2 NDUFC2-KCTD14 NDUFS1 NDUFS2 NDUFS3 NDUFS4 NDUFS5 NDUFS6 NDUFS7 NDUFS8 NDUFV1 NDUFV2 NDUFV3 NRF1 NRF2 PPA1 PPA2 SDHA SDHB SDHC SDHD TCIRG1 TFAM UQCR10 UQCR11 UQCRB UQCRC1 UQCRC2 UQCRFS1 UQCRH UQCRHL UQCRQ YY1
F19: TCA cycle (1) (accession: hsa00020)	included	included	included	ACLY ACO1 ACO2 CS DLAT DLD DLST FH IDH1 IDH2 IDH3A IDH3B IDH3G MDH1 MDH2 OGDH OGDHL PC PCK1 PCK2 PDHA1 PDHA2 PDHB SDHA SDHB SDHC SDHD SUCLA2 SUCLG1 SUCLG2
F20: Apoptosis (1) (accession: hsa04210)	included	included	included	ACTB ACTG1 AIFM1 AKT1 AKT2 AKT3 APAF1 ATF4 ATM BAD BAK1 BAX BBC3 BCL2 BCL2A1 BCL2L1 BCL2L11 BID BIRC2 BIRC3 BIRC5 CAPN1 CAPN2 CASP10 CASP12 CASP2 CASP3 CASP6 CASP7 CASP8 CASP9 CFLAR CHUK CSF2RB CTSB CTSC CTSD CTSF CTSH CTSK CTSL CTSO CTSS CTSV CTSW CTSZ CYCS DAB2IP DAXX DDIT3 DFFA DFFB DIABLO EIF2AK3 EIF2S1 ENDOG ERN1 FADD FAS FASLG FOS GADD45A GADD45B GADD45G GZMB HRAS HRK HTRA2 IKBKB IKBKG IL3 IL3RA ITCH ITPR1 ITPR2 ITPR3 JUN KRAS LMNA LMNB1 LMNB2 MAP2K1 MAP2K2 MAP3K14

				MAP3K5 MAPK1 MAPK10 MAPK3 MAPK8 MAPK9 MCL1 NFKB1 NFKBIA NGF NRAS NTRK1 PARP1 PARP2 PARP3 PARP4 PDPK1 PIDD1 PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PMAIP1 PRF1 PTPN13 RAF1 RELA RIPK1 SEPTIN4 SPTA1 SPTAN1 TLR4 TNF TNFRSF10A TNFRSF10B TNFRSF1A TNFSF10 TP53 TP53AIP1 TRADD TRAF1 TRAF2 TUBA1A TUBA1B TUBA1C TUBA3C TUBA3D TUBA3E TUBA4A TUBA8 TUBAL3 VIM XIAP
F21: Hippo signaling (1,13) (accession: hsa04390)	included	included	included	ACTB ACTG1 AFP AJUBA AMH AMOT APC APC2 AREG AXIN1 AXIN2 BBC3 BIRC2 BIRC3 BIRC5 BMP2 BMP4 BMP5 BMP6 BMP7 BMP8A BMP8B BMPR1A BMPR1B BMPR2 BTRC CCN2 CCND1 CCND2 CCND3 CDC42 CDH1 CRB1 CRB2 CSNK1D CSNK1E CTNNA1 CTNNA2 CTNNA3 CTNNB1 DLG1 DLG2 DLG3 DLG4 DLG5 DVL1 DVL2 DVL3 FBXW11 FGF1 FRMD1 FRMD6 FZD1 FZD10 FZD2 FZD3 FZD4 FZD5 FZD6 FZD7 FZD8 FZD9 GDF5 GDF6 GDF7 GLI2 GSK3B ID1 ID2 ITGB2 KIBRA LATS1 LATS2 LEF1 LIMD1 LLGL1 LLGL2 MOB1A MOB1B MST1 MST2 MYC NF2 NKD1 NKD2 PALS1 PARD3 PARD6A PARD6B PARD6G PATJ PPP1CA PPP1CB PPP1CC PPP2CA PPP2CB PPP2R1A PPP2R1B PPP2R2A PPP2R2B PPP2R2C PPP2R2D PRKACA PRKCI PRKCZ RASSF1 RASSF6 RHOA RHOB SAV1 SCRIB SERPINE1 SMAD1 SMAD2 SMAD3 SMAD4 SMAD7 SNAI2 SOX2 STK3 TCF7 TCF7L1 TCF7L2 TEAD1 TEAD2 TEAD3 TEAD4 TGFB1 TGFB2 TGFB3 TGFB1 TGFB2 TP53BP2 TP73 TPTEP2-CSNK1E WNT1 WNT10A WNT10B WNT11 WNT16 WNT2 WNT2B WNT3 WNT3A WNT4 WNT5A WNT5B WNT6 WNT7A WNT7B WNT8A WNT8B WNT9A WNT9B WTIP WWC1 WWTR1 YAP1 YWHAB YWHAE YWHAG YWHAH YWHAQ YWHAZ
F22: ECM interaction (1) (accession: hsa04512)	included	included	included	AGRN CD36 CD44 CD47 CHAD COL1A1 COL1A2 COL2A1 COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6 COL6A1 COL6A2 COL6A3 COL6A5 COL6A6 COL9A1 COL9A2 COL9A3 COMP DAG1 DMP1 DSPP FN1 FRAS1 FREM1 FREM2 GP1BA GP1BB GP5 GP6 GP9 HMMR HSPG2 IBSP ITGA1 ITGA10 ITGA11 ITGA2 ITGA2B ITGA3 ITGA4 ITGA5 ITGA6 ITGA7 ITGA8 ITGA9 ITGAV ITGB1 ITGB3 ITGB4 ITGB5 ITGB6 ITGB7 ITGB8 LAMA1 LAMA2 LAMA3 LAMA4 LAMA5 LAMB1 LAMB2 LAMB3 LAMB4 LAMC1 LAMC2 LAMC3 MEPE NPNT RELN SDC1 SDC4 SPP1 SV2A SV2B SV2C THBS1 THBS2 THBS3 THBS4 TNC TNN TNR TNXB VTN VWF
F23: Complement (14)	excluded	included	excluded	C1QB C1QC C1R C1S C2 C3 C4 C5 C6 C7 C8 C9

F24: JAK-STAT pathway (1) (accession: hsa04630)	included	included	included	AKT1 AKT2 AKT3 AOX1 BCL2 BCL2L1 CCND1 CCND2 CCND3 CDKN1A CISH CLCF1 CNTF CNTFR CREBBP CRLF2 CSF2 CSF2RA CSF2RB CSF3 CSF3R CSH1 CSH2 CTF1 EGF EGFR EP300 EPO EPOR FHL1 GFAP GH1 GH2 GHR GRB2 HRAS IFNA1 IFNA10 IFNA13 IFNA14 IFNA16 IFNA17 IFNA2 IFNA21 IFNA4 IFNA5 IFNA6 IFNA7 IFNA8 IFNAR1 IFNAR2 IFNB1 IFNE IFNG IFNGR1 IFNGR2 IFNK IFNL1 IFNL2 IFNL3 IFNLR1 IFNW1 IL10 IL10RA IL10RB IL11 IL11RA IL12A IL12B IL12RB1 IL12RB2 IL13 IL13RA1 IL13RA2 IL15 IL15RA IL19 IL2 IL20 IL20RA IL20RB IL21 IL21R IL22 IL22RA1 IL22RA2 IL23A IL23R IL24 IL26 IL27 IL27RA IL2RA IL2RB IL2RG IL3 IL31 IL31RA IL3RA IL4 IL4R IL5 IL5RA IL6 IL6R IL6ST IL7 IL7R IL9 IL9R IRF9 JAK1 JAK2 JAK3 LEP LEPR LIF LIFR MCL1 MPL MTOR MYC OSM OSMR PDGFA PDGFB PDGFRA PDGFRB PIAS1 PIAS2 PIAS3 PIAS4 PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PIM1 PRL PRLR PTPN11 PTPN2 PTPN6 RAF1 SOCS1 SOCS2 SOCS3 SOCS4 SOCS5 SOCS6 SOCS7 SOS1 SOS2 STAM STAM2 STAT1 STAT2 STAT3 STAT4 STAT5A STAT5B STAT6 THPO TSLP TYK2
F25: Chemokines (1, 5) (accession: hsa04062)	included	included	included	ADCY1 ADCY2 ADCY3 ADCY4 ADCY5 ADCY6 ADCY7 ADCY8 ADCY9 AKT1 AKT2 AKT3 ARRB1 ARRB2 BAD BCAR1 BRAF CCL1 CCL11 CCL13 CCL14 CCL15 CCL16 CCL17 CCL18 CCL19 CCL2 CCL20 CCL21 CCL22 CCL23 CCL24 CCL25 CCL26 CCL27 CCL28 CCL3 CCL3L1 CCL3L3 CCL4 CCL4L1 CCL4L2 CCL5 CCL7 CCL8 CCR1 CCR10 CCR2 CCR3 CCR4 CCR5 CCR6 CCR7 CCR8 CCR9 CDC42 CHUK CRK CRKL CX3CL1 CX3CR1 CXCL1 CXCL10 CXCL11 CXCL12 CXCL13 CXCL14 CXCL16 CXCL2 CXCL3 CXCL5 CXCL6 CXCL8 CXCL9 CXCR1 CXCR2 CXCR3 CXCR4 CXCR5 CXCR6 DOCK2 ELMO1 FGR FOXO3 GNAI1 GNAI2 GNAI3 GNAQ GNB1 GNB2 GNB3 GNB4 GNB5 GNG10 GNG11 GNG12 GNG13 GNG2 GNG3 GNG4 GNG5 GNG7 GNG8 GNGT1 GNGT2 GRB2 GRK1 GRK2 GRK3 GRK4 GRK5 GRK6 GRK7 GSK3A GSK3B HCK HRAS IKBKB IKBKG ITK JAK2 JAK3 KRAS LYN MAP2K1 MAPK1 MAPK3 NCF1 NFKB1 NFKBIA NFKBIB NRAS PAK1 PARD3 PF4 PF4V1 PIK3CA PIK3CB PIK3CD PIK3CG PIK3R1 PIK3R2 PIK3R3 PIK3R5 PIK3R6 PLCB1 PLCB2 PLCB3 PLCB4 PLCG1 PLCG2 PPBP PREX1 PRKACA PRKACB PRKACG PRKCB PRKCD PRKCZ PTK2 PTK2B PXN RAC1 RAC2 RAC3 RAF1 RAP1A RAP1B RASGRP2 RELA RHOA ROCK1 ROCK2 SHC1 SHC2 SHC3 SHC4 SOS1 SOS2 SRC STAT1 STAT2 STAT3 STAT5B TIAM1 VAV1 VAV2 VAV3 WAS XCL1 XCL2 XCR1
F26: VEGF signaling (1)	included	included	included	AKT1 AKT2 AKT3 BAD CASP9 CDC42 HRAS HSPB1 JMJD7-PLA2G4B KDR KRAS MAP2K1 MAP2K2 MAPK1 MAPK11 MAPK12 MAPK13 MAPK14 MAPK3 MAPKAPK2

(accession: hsa04370)				MAPKAPK3 NFATC2 NOS3 NRAS PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PLA2G4A PLA2G4B PLA2G4C PLA2G4D PLA2G4E PLA2G4F PLCG1 PLCG2 PPP3CA PPP3CB PPP3CC PPP3R1 PPP3R2 PRKCA PRKCB PRKCG PTGS2 PTK2 PXN RAC1 RAC2 RAC3 RAF1 SH2D2A SHC2 SPHK1 SPHK2 SRC VEGFA
F27: Fatty acid (FA) metabolism (1, 5, 6, 9, 10) (accession: hsa01212)	included	included	included	ACAA1 ACAA2 ACADL ACADM ACADS ACADSB ACADVL ACAT1 ACAT2 ACOX1 ACOX3 ACSL1 ACSL3 ACSL4 ACSL5 ACSL6 ADH1A ADH1B ADH1C ADH4 ADH5 ADH6 ADH7 ADHFE1 ALDH1A3 ALDH1B1 ALDH2 ALDH3A1 ALDH3A2 ALDH7A1 ALDH9A1 APOC1 APOC2 APOC3 CD36 CPT1A CPT1B CPT1C CPT2 CYP4A11 CYP4A22 ECHS1 EHHADH ESRRA FABP1 FABP2 FABP3 FABP4 FABP5 FABP6 FASN FOXA2 GCDH GPX1 HADH HADHA HADHB HSD17B10 HSD17B4 LPL NR1H2 NR1H3 PDK4 PPARA SCD1 SLC27A1 SLC27A2 SLC27A3 SLC27A4 SLC27A5 SLC27A6 SOD2 SREBF1 TRB3
F28: Curroptosis (15)	included	included	included	ACO2 AIF ATP7A ATP7B CDKN1A DLAT ENO3 FDX1 FDXR FXN GLS2 GLUT1 GLUT12 GLUT3 GLUT4 HK2 ISCU LDHA LIAS LPIN1 MLYCD PDK2 PFK1 PFKFB3 PFKFB4 PGAM1 PRKN SCO2 SESN1 SESN2 SLC1A3 SLC31A1 SLC7A11 SREBF2 TIGAR TP53
F29: ER stress (1, 5, 6) (accession: hsa04141)	included	included	included	AMFR ATF4 ATF6 ATF6B ATXN3 ATXN3L BAG1 BAG2 BAK1 BAX BCAP31 BCL2 CALR CANX CAPN1 CAPN2 CASP12 CKAP4 CRYAA CRYAB CUL1 DAD1 DDIT3 DDOST DERL1 DERL2 DERL3 DNAJA1 DNAJA2 DNAJB1 DNAJB11 DNAJB12 DNAJB2 DNAJC1 DNAJC10 DNAJC3 DNAJC5 DNAJC5B DNAJC5G EDEM1 EDEM2 EDEM3 EIF2AK3 EIF2S1 ERLEC1 ERN1 ERO1A ERO1B ERP29 FBXO2 FBXO6 GANAB HERPUD1 HSP90AA1 HSP90AB1 HSP90B1 HSPA1A HSPA1B HSPA1L HSPA4L HSPA5 HSPA6 HSPA8 HSPBP1 HSPH1 HYOU1 LMAN1 LMAN1L LMAN2 MAGT1 MAN1A1 MAN1A2 MAN1B1 MAN1C1 MAP2K7 MAP3K5 MAPK10 MAPK8 MAPK9 MARCHF6 MBTPS1 MBTPS2 MMP24-AS1-EDEM2 MOGS NFE2L2 NGLY1 NPLOC4 NSFL1C OS9 OSTC P4HB PDIA3 PDIA4 PDIA6 PLAA PPP1R15A PREB PRKCSH PRKN RAD23A RAD23B RBX1 RNF185 RNF5 RPN1 RPN2 RRBP1 SAR1A SAR1B SEC13 SEC23A SEC23B SEC24A SEC24B SEC24C SEC24D SEC31A SEC31B SEC61A1 SEC61A2 SEC61B SEC61G SEC62 SEC63 SEL1L SEL1L2 SELENOS SIL1 SKP1 SSR1 SSR2 SSR3 SSR4 STT3A STT3B STUB1 SVIP SYVN1 TMEM258 TRAF2 TRAM1 TRAM1L1 TUSC3 TXNDC5 UBE2D1 UBE2D2 UBE2D3 UBE2D4 UBE2G1 UBE2G2 UBE2J1 UBE2J2 UBE4B UBQLN1 UBQLN2

				UBQLN3 UBQLN4 UBXN1 UBXN2A UBXN4 UBXN6 UBXN8 UFD1 UGGT1 UGGT2 VCP WFS1 XBP1 YOD1
F30: Bile acid metabolism (1, 16) (accession: hsa04976)	excluded	excluded	included	ABCB1 ABCB11 ABCB4 ABCC1 ABCC2 ABCC3 ABCC4 ABCC5 ABCG2 ABCG5 ABCG8 ADCY1 ADCY2 ADCY3 ADCY4 ADCY5 ADCY6 ADCY7 ADCY8 ADCY9 AQP1 AQP4 AQP8 AQP9 ATP1A1 ATP1A2 ATP1A3 ATP1A4 ATP1B1 ATP1B2 ATP1B3 ATP1B4 BAAT CA2 CFTR CREB1 CYP27A1 CYP2A2 CYP2C70 CYP3A4 CYP7A1 CYP7B1 CYP8B1 EPHX1 FGF15 FGF19 FGFR4 FXR FXD2 GLP1R GNAS GSK3B HMGCR KCNN2 LCAT LDLR MTTP NCEH1 NR0B2 NR1H4 NR5A2 OSTB PEPCK PPARA PPARGC1B PRKACA PRKACB PRKACG RXRA SCARB1 SCT SCTR SHP SLC10A1 SLC10A2 SLC22A1 SLC22A7 SLC22A8 SLC27A5 SLC2A1 SLC4A2 SLC4A4 SLC4A5 SLC51A SLC51B SLC5A1 SLC9A1 SLC9A3 SLC01A1 SLC01A2 SLCO1B1 SLCO1B2 SLCO1B3 SREBF1 STAT3 SULT2A1 UGT1A1 UGT1A10 UGT1A3 UGT1A4 UGT1A5 UGT1A6 UGT1A7 UGT1A8 UGT1A9 UGT2A1 UGT2A2 UGT2A3 UGT2B10 UGT2B11 UGT2B15 UGT2B17 UGT2B28 UGT2B4 UGT2B7
F31: Focal adhesion (1) (accession: hsa04510)	included	included	included	ACTB ACTG1 ACTN1 ACTN4 AKT1 AKT2 AKT3 ARHGAP35 ARHGAP5 BAD BCAR1 BCL2 BIRC2 BIRC3 BRAF BUB1B- PAK6 CAPN2 CAV1 CAV2 CAV3 CCND1 CCND2 CCND3 CDC42 CHAD COL1A1 COL1A2 COL2A1 COL4A1 COL4A2 COL4A3 COL4A4 COL4A5 COL4A6 COL6A1 COL6A2 COL6A3 COL6A5 COL6A6 COL9A1 COL9A2 COL9A3 COMP CRK CRKL CTNNB1 DIAPH1 DOCK1 EGF EGFR ELK1 EMP1 EMP2 ERBB2 FLNA FLNB FLNC FLT1 FLT4 FN1 FYN GRB2 GSK3B HGF HRAS IBSP IGF1 IGF1R ILK ITGA1 ITGA10 ITGA11 ITGA2 ITGA2B ITGA3 ITGA4 ITGA5 ITGA6 ITGA7 ITGA8 ITGA9 ITGAV ITGB1 ITGB3 ITGB4 ITGB5 ITGB6 ITGB7 ITGB8 JUN KDR LAMA1 LAMA2 LAMA3 LAMA4 LAMA5 LAMB1 LAMB2 LAMB3 LAMB4 LAMC1 LAMC2 LAMC3 MAP2K1 MAPK1 MAPK10 MAPK3 MAPK8 MAPK9 MET MYL10 MYL11 MYL12A MYL12B MYL2 MYL5 MYL7 MYL9 MYLK MYLK2 MYLK3 MYLK4 PAK1 PAK2 PAK3 PAK4 PAK5 PAK6 PARVA PARVB PARVG PDGFA PDGFB PDGFC PDGFD PDGFRA PDGFRB PDPK1 PGF PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PIP5K1A PIP5K1B PIP5K1C PPP1CA PPP1CB PPP1CC PPP1R12A PPP1R12B PPP1R12C PRKCA PRKCB PRKCG PTEN PTK2 PXN RAC1 RAC2 RAC3 RAF1 RAP1A RAP1B RAPGEF1 RASGRF1 RELN RHOA ROCK1 ROCK2 SHC1 SHC2 SHC3 SHC4 SOS1 SOS2 SPP1 SRC THBS1 THBS2 THBS3 THBS4 TLN1 TLN2 TNC TNN TNR TNXB VASP VAV1 VAV2 VAV3 VCL VEGFA VEGFB VEGFC VEGFD VTN VWF XIAP ZYX

F32: Glucose metabolism (1) (accession: hsa00010)	included	included	included	ACSS1 ACSS2 ADH1A ADH1B ADH1C ADH4 ADH5 ADH6 ADH7 ADPGK AKR1A1 ALDH1B1 ALDH2 ALDH3A1 ALDH3A2 ALDH3B1 ALDH3B2 ALDH7A1 ALDH9A1 ALDOA ALDOB ALDOC BPGM DLAT DLD ENO1 ENO2 ENO3 ENO4 FBP1 FBP2 G6PC1 G6PC2 G6PC3 GALM GAPDH GAPDHS GCK GPI HK1 HK2 HK3 HKDC1 LDHALDHAL6A LDHAL6B LDHB LDHC MINPP1 PCK1 PCK2 PDHA1 PDHA2 PDHB PFKL PFKM PFKP PGAM1 PGAM2 PGAM4 PGK1 PGK2 PGM1 PGM2 PKLR PKM TPI1
F33: Hepatocellular carcinoma (1) (accession: hsa05225)	included	included	included	ACTB ACTG1 ACTL6A ACTL6B AKT1 AKT2 AKT3 APC APC2 ARAF ARID1A ARID1B ARID2 AXIN1 AXIN2 BAD BAK1 BAX BCL2L1 BRAF BRD7 CCND1 CDK4 CDK6 CDKN1A CDKN2A CSNK1A1 CSNK1A1L CTNNB1 DDB2 DPF1 DPF3 DVL1 DVL2 DVL3 E2F1 E2F2 E2F3 EGFR ELK1 FRAT1 FRAT2 FZD1 FZD10 FZD2 FZD3 FZD4 FZD5 FZD6 FZD7 FZD8 FZD9 GAB1 GADD45A GADD45B GADD45G GRB2 GSK3B GSTA1 GSTA2 GSTA3 GSTA4 GSTA5 GSTM1 GSTM2 GSTM3 GSTM4 GSTM5 GSTO1 GSTO2 GSTP1 GSTT1 GSTT2 GSTT2B HGF HMOX1 HRAS IGF1R IGF2 KEAP1 KRAS LEF1 LRP5 LRP6 MAP2K1 MAP2K2 MAPK1 MAPK3 MET MGST1 MGST2 MGST3 MTOR MYC NFE2L2 NQO1 NRAS PBRM1 PHF10 PIK3CA PIK3CB PIK3CD PIK3R1 PIK3R2 PIK3R3 PLCG1 PLCG2 POLK PRKCA PRKCB PRKCG PTEN RAF1 RB1 RPS6KB1 RPS6KB2 SHC1 SHC2 SHC3 SHC4 SMAD2 SMAD3 SMAD4 SMARCA2 SMARCA4 SMARCB1 SMARCC1 SMARCC2 SMARCD1 SMARCD2 SMARCD3 SMARCE1 SOS1 SOS2 TCF7 TCF7L1 TCF7L2 TERC TERT TGFA TGFB1 TGFB2 TGFB3 TGFB1R TGFB2R TP53 TXNRD1 TXNRD2 TXNRD3 WNT1 WNT10A WNT10B WNT11 WNT16 WNT2 WNT2B WNT3 WNT3A WNT4 WNT5A WNT5B WNT6 WNT7A WNT7B WNT8A WNT8B WNT9A WNT9B
F34: MASLD-associated genes (17)	included	included	included	ABHD5 APOB GCKR HSD17B13 IFNL4 IL28B MAR1 MBOAT7 MERTK PCSK7 PEMT PNPLA3 PPP1R3B SERPINA1 SOD2 TERT TM6SF2 UCP2
F35: Wnt signaling (1) (accession: hsa04310)	included	included	included	APC APC2 APCDD1 APCDD1L AXIN1 AXIN2 BAMBI BTRC CACYBP CAMK2A CAMK2B CAMK2D CAMK2G CBY1 CCAR2 CCDC88C CCN4 CCND1 CCND2 CCND3 CER1 CHD8 CREBBP CSNK1A1 CSNK1A1L CSNK1E CSNK2A1 CSNK2A2 CSNK2A3 CSNK2B CTBP1 CTBP2 CTNNB1 CTNNBIP1 CTNND2 CUL1 CXXC4 DAAM1 DAAM2 DKK1 DKK2 DKK4 DVL1 DVL2 DVL3 EP300 FBXW11 FOSL1 FRAT1 FRAT2 FRZB FZD1 FZD10 FZD2 FZD3 FZD4 FZD5 FZD6 FZD7 FZD8 FZD9 GPC4 GSK3B INVS JUN LEF1

				LGR4 LGR5 LGR6 LRP5 LRP6 LZTS2 MAP3K7 MAPK10 MAPK8 MAPK9 MCC MMP7 MYC NFATC1 NFATC2 NFATC3 NFATC4 NKD1 NKD2 NLK NOTUM PLCB1 PLCB2 PLCB3 PLCB4 PORCN PPARD PPP3CA PPP3CB PPP3CC PPP3R1 PPP3R2 PRICKLE1 PRICKLE2 PRICKLE3 PRICKLE4 PRKACA PRKACB PRKACG PRKCA PRKCB PRKCG PSEN1 RAC1 RAC2 RAC3 RBX1 RHOA RNF43 ROCK2 ROR1 ROR2 RSPO1 RSPO2 RSPO3 RSPO4 RUVBL1 RYK SENP2 SERPINF1 SFRP1 SFRP2 SFRP4 SFRP5 SIAH1 SIRT1 SKP1 SMAD3 SMAD4 SOST SOX17 TBL1X TBL1XR1 TBL1Y TCF7 TCF7L1 TCF7L2 TLE1 TLE2 TLE3 TLE4 TLE6 TLE7 TP53 TPTEP2-CSNK1E VANGL1 VANGL2 WIF1 WNT1 WNT10A WNT10B WNT11 WNT16 WNT2 WNT2B WNT3 WNT3A WNT4 WNT5A WNT5B WNT6 WNT7A WNT7B WNT8A WNT8B WNT9A WNT9B ZNRF3
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Table S4: DEGs in MASH versus NonMASH in distinct ROIs from our GeoMx DSP dataset for 35 MASH-associated pathway gene sets curated from the KEGG database and published literature. DEGs are selected when P value is less than 0.05 and a fold change of "MASH_{expr}" over "NonMASH_{expr}" is greater than 1.5 or less than 1/1.5, where MASH_{expr} or NonMASH_{expr} represents average gene expression from MASH subjects or NonMASH subjects, respectively. Bold represents FDR < 0.25.

ROI types	Differential gene expression in MASH versus NonMASH	DEGs
Vin ^{en} ROI	Increased	IL32 CYP2A6 VIM FABP4 COL4A6 CCL21 CACNA2D3 ACKR3 S100A9 MTOR ID1 SPARC SFRP5 JUND ENO3 AKT3 CTSS GSTP1 HFE COL4A1 ZYX RET COL4A2 PRICKLE4 RAB33B GRK5 FBN1 EMP3 VASP CXCL12 CSNK1A1L
CD45 ^{en} ROI	Increased	IGHG1 IGKC CD74 COL3A1 VIM CTSS DCN C1QB C1QC IL32 FTH1 RPLP1 RPS19 CD68 MOB1A LYZ GPX1 HSPA8 CCL2 RPL31 RPL37 CTSZ RPS13 RPS27 MYL12A RPS14 RPL13 RPL28 RPL41 RPS29 RPL8 MYL9 RPS21 HSPA1A RPL11 CTSD ITGB2 RPL37A RPS18 COL4A1 RPS12 RPS6 RPS28 ATG13 TUBA1C RPS25 RPL32 RPL23 RPL34 RPL21 RPL18 RPS9 MAP3K8 ITGB1 RPS2 RPLP2 ID1 RPS27A RPS16 RPL9 H2AC21 RPLP0 RPS15A GNAI2 GORASP1 VAMP8 RPS17 DAPK3 SQSTM1 RPS20 RPS3A RPS4X RPL30 CETP RPS15 CTNNA1 ELK1 RPL36 JUND PXN SIN3A UBA52 RPL19 CTSH RPS26 RPS7 RPL18A RPL7 RPS8 RPL26 KLF2 RPL15 RPL5 RPL39 PPIA HSPB1 ID3 RPL7A KDR RPL35A HSP90AB1 RPL12 RPS3 LTB ACSL4
Alb ^{en} ROI	Increased	IL32 CYP2A6 SPP1 AHR ALDH1A3 FABP4 GNB3 ALDH3B1 PRICKLE4 PPP2R2B PRAP1 SSR2 NFKB2 CRK TAX1BP1 TNFRSF4 LDLR BMP8A LEF1 PLCD1 SPHK2 GLS SLC25A4 DUSP5 ICAM1 LDHAL6A KLF10 CSNK1A1L SQSTM1 IL20RA RNF43 NR1H2 LPAR6 TNFAIP3 CACNA2D3 MINPP1 INHBC VWF TP53BP2 SIRT1 UVRAG DNAJC5G ATG13 ACLY MDM2
Vin ^{en} ROI	Decreased	RAC3 TNFSF8 FBXW11 SMARCD2 PFKFB3 RRAS TNFRSF10A SOX17 CREB3 AHR PLIN2 GPT2 GNG3 TAX1BP1 PTPN13 WNT8A IRS2 GLUL AOX1 CYP3A4 CYP2C19 CYP1A2
CD45 ^{en} ROI	Decreased	IL26 ACVR1 AMH IFNE MAPK12 SELE GP6 PRKCZ GP5 GNGT2 GADD45G CYP2C19 CAV3 KIT CREB3
Alb ^{en} ROI	Decreased	IFNA2 HMGB1 PPP2R5C RPL7 RPL17 ATP6V1G1 RPL36A TBL1X RPS3A RPS20 NDUFB7 E2F1 UQCRC1 IL1RAP RPS5 PGF BMP4 ATF2 PITX2 ACVR2B SDHC RPL26 TLN1 CHUK VCAM1 GSTO1 CXCL16 CCL3 ACO1 CCR1 RPS6 RPS23 RPL22 RPL32 CP RPL19 RPL34 PPARGC1A RPL10A GLS2 RPL6 AGXT CYP2C19 RPL38 COX6A2 CD4 IRS2 ITGA9 RELN SERPINA1 CETP IGF2 ACADSB LPA G6PC1 CCL14 PCK1

Table S5: DEGs associated with neutrophil recruitment and inflammatory pathways in MASH vs. NonMASH and MASH-HF vs. MASH-LF. Summary of significant gene expression changes (FDR < 0.25) across the primary comparison groups: MASH vs. NonMASH and MASH-HF vs. MASH-LF. Genes are categorized by neutrophil activation and immune/B cell signaling. MHC, major histocompatibility complex.

Category	Gene symbol	Comparison	ROI	Log ₂ FC	FDR	Key function & characteristics
Neutrophil	<i>S100A6</i>	HF vs. LF	CD45	+1.49	0.172	Marker for neutrophil infiltration and activation
Immune / B cell	<i>CD74</i>	MASH vs. NonMASH	CD45	+3.48	0.027	MHC class II antigen presentation, pro-inflammatory
	<i>IGKC</i>	HF vs. LF	CD45	+3.70	0.084	Marker for B cell and humoral immune response
	<i>IGHG1</i>	MASH vs. NonMASH	CD45	+3.89	0.216	Immunoglobulin heavy chain activation
		HF vs. LF		+2.71	0.119	

Table S6: DEGs in MASH-HF versus MASH-LF in distinct ROIs from our GeoMx DSP dataset for 35 MASH-associated pathway gene sets curated from the KEGG database and published literature. DEGs are selected when P value is less than 0.05 and a fold change of "MASH-HF_{expr}" over "MASH-LF_{expr}" is greater than 1.5 or less than 1/1.5, where MASH-HF_{expr} or MASH-LF_{expr} represents average gene expression from MASH-HF subjects or MASH-LF subjects, respectively. Bold represents FDR < 0.25.

ROI types	Differential gene expression in MASH-HF versus MASH-LF	DEGs
Vin ^{en} ROI	Increased	ACVR1C NOS1 CCL3L3 WNT8A DDO FGF18 GNG3 PPP1R12A WNT3A WNT8B TNXB MAPK8 FABP6 COX6A2 WFS1 RASGRP3 EFNA3 CYP27B1 RASGRP4 TNFSF11 CCL28 MAP3K6 TNFRSF4 CTSW CYP11B2 FZD2 GH1 TEAD3 MAPKAPK5 GP5 ITGA3 CIDEA ITPR3 SOCS6 EPHA2 TUBA3C CASP10 BAK1 TNFRSF13C GDF2 PIAS2 BRAF PDGFRA ANGPT2 SOCS1 CXCR2 MACROH2A2 BIRC2 SOX17 CASP6 GPBAR1 PITX2 PF4 ITGA2B CRB2 SMARCC2 TNFSF8 FGFR1 STX17 CCL17 COL4A2 CD44 CSF2RA TNFRSF10C TNFRSF19 RB1CC1 RASSF1 FGF16 BIRC5 IL10 MAPK12 KLF16 VPS18 NTF3 TGIF1 EFNA4 MAP3K14 RRAGC ZNRF3 ADCY5 LATS1 FGF17 TLR2 IL27
CD45 ^{en} ROI	Increased	DNAJB1 IL2RG ATF2 RELT SOCS3 GDF1 WNT8A AMHR2 IL9R COL1A2 GGT5 CD44 RRAS IGKC ACTN4 JUND ANGPT2 KLF4 PKN3 PPP1R15A TNFSF12 ADCY5 TNFRSF6B IGHG1 RASGRP4 CRKL RASA2 DUSP2 RAC2 APC2 KLF2 ATG12 TNFRSF13C PRKCD UBQLN4 E2F4 PTPN6 XCL1 AGPAT1 S100A6 PIK3CD LPAR2 PPP2R2A ATG5 GNG7 WFS1 CACNA1E PMAIP1 ELMO1 CRB2 GP5 TNFRSF13B LAMC3 FADD GNG11 KLF6 LYN KLF16 HRAS H2AC14 CER1 PITX2 CIDEA
Alb ^{en} ROI	Increased	FOS PCK1 HSPA1A VIM WIP1 GNG10 IL3RA TAOK1 PFKFB3 RAC2 COL1A2 SGK1 ELMO1 PPARGC1A RRAS ARHGAP5 WNT3 MYC NR4A1 SOD2 VASP CTSL CHAD ARID1B BRAF ANGPTL4 ATP6V1B2 CXCL9 FBXW11 MEF2C SRC RPS24 RPL13 GNGT2 TLN1 RPL22 LPA WNT8A KLF16 EFNA1 CYP4F3 GYS1 RPL9 HSP90AA1 UGGT1 CD44 TBK1 AGPAT1 NRAS RPS2 IFNGR1 SRF EIF4E2
Vin ^{en} ROI	Decreased	UQCRC2 FZD5 NTRK2 IL6R COX17 FBXO2 PPP2R1B SEL1L ERN1 GNG12 GNAI2 EP300 PIK3R1 IFNA6 SMPD1 FDX1 NDUFB6 CTSF ATG13 MAPK10 LEPR SLC31A1 CTNNB1 SREBF2 GLUL ULK1 NDUFA2 PIAS4 MAP3K2 ATP6V0D1 UBXN6 AKT2 HSPA8 PLIN2 RPL39 MGST2 RPL35 SEC62 GSTK1 RPL31 NFKBIB HSPB1 ADCY8 VAV2 ATP6V0E1 OPTN WNT5B NDUFB8 ATP5PD WNT10A HJV RPS15A YWHAE PIAS1 SP3 RPN1 COL9A1 GSTA3 SH2D2A COX5A NF1 RPL14 ATP5MG RPS2 CALCOCO2 RPL23 PRKCSH ACAT2 RPS5 SDHD GRB2 RPS3A OS9 DEPTOR DNAJA1 TMEM258 COL4A6 MLXIPL COX6B1 RPL8 KLF9 NDUFV2 ADH6 ARRB2 LGR6 RPL10A COX7B DUSP3 HPGD SCO2 NDUFA11 RPL12 SREBF1 GPT ARAF MYL9 RAF1 HSP90AA1 UQCR10 CPT2 FZD6 PXN RPL15 HADH RPL22 UBE2D3 CYP2J2 VEGFB RPL34 CTNND2 PC SQSTM1 SLC25A5 GCKR VCP SEC61G LCAT NDUFB4

		RPL4 ITGA6 HADHA ITGB5 PDIA3 UQCRB CYP51A1 MDH1 DNAJC1 AKR1C3 PDIA6 PPIA NFKBIA PRKACA ASL IDH2 SKP1 RPS29 ITGA1 RPL27 GSTA2 PNPLA3 LMAN1 STAT6 TUBA3D NDUFB9 ATP5F1C RPLP2 CSF1R SDC1 MST1 PCK2 ATP5F1A H2AC4 RPL26 CRLF2 HADHB MAN1A1 NDUFB2 ATP5ME SOD2 PLB1 UBXN1 SUCLG1 SDHA RPS8 ATP6V1G1 MAGT1 CYP4F3 CXCR4 NDUFS5 RPL36 IDH1 IL32 ATP5MF UBA52 IL6ST RPS23 DGAT1 NDUFV1 SLC27A2 ATP5MC2 RPS19 HSD17B10 ENO3 CD14 NDUFA1 COX7C RAP1A RPS13 CTSD COX6C HSP90B1 CYP4V2 SAR1B RPL9 LAMP2 RPLP1 DLAT PDK4 NDUFB1 FH SSR4 NDUFA13 RPS18 CYP2B6 ATP5PO RPL24 NDUFA4 HNF4A RPL11 RPL38 RPS17 PLCB1 LAMP1 GPX4 PDIA4 FASN RXRA GLUD1 RPS20 CYP4F2 NR1I3 RPS9 LDHA RPN2 RPS27 UQCRC1 RPL32 RPS11 RPS6 CBR1 GSTO1 ID2 GABARAP TRAM1 ALDH1B1 GPX1 RPL41 RPL19 PYGL COX4I1 AOX1 ATP5MC3 ACSL1 RPS15 EHHADH MGST3 PEMT RPLP0 ACADVL COX6A1 SLC27A5 OTC RPL28 ACY1 RPL13 RPS21 RPS25 UQCR11 CANX ACADM EPHX2 SDHB RPS16 TNFSF10 ALDH3A2 MDH2 G6PC1 RPS14 ALDH9A1 TFR2 RPL18 CYP27A1 CYP3A5 COX5B AGT RPL27A ATP5F1B RPL30 RRBP1 ATP5F1D CYP8B1 RPS28 TDO2 GHR ACADS CYP4F12 ATP5PF CYP2C8 RPS12 HSD17B4 IGF2 CALR ABATACAA1 RPL37 RPL37A PRAP1 CTSB ACADSB UQCRQ P4HB ASS1 CPS1 COX8A GOT2 HSD17B13 GLS2 CYP2D6 CYP2C9 XBP1 RPL29 ECHS1 ACAA2 ARG1 MGST1 ADH4 PCK1 FTH1 CTSZ SERPINF1 PTGR1 CP ACAT1 CYP4A22 ALDH4A1 GSTA1 APOB ADH1A GSTM1 HPD CYP2E1 FN1 FABP1 ALDH2 SERPINA1 AGXT VTN TF APOE APOC3 APOA1 ADH1B APOH C3 ALDOB
CD45 ^{en} ROI	Decreased	GHR ACADS CYP8B1 ECHS1 C9 MGST1 CPS1 ALDH4A1 IL6R TNFSF10 GOT2 PEMT ACADSB ACAA2 IDH2 ITGA6 SUCLG1 RPN1 GSTO1 TRAM1 ACADM ALDH3A2 RRBP1 HSD17B13 OTC ACSL1 C1R ALDH2 ALDOB ADH1B ACAT1 CP APOC1 APOC2 APOC3 APOH HPD TF C3 FDX1 C2 ADH1A VTN ATF6B XBP1 ACY1 CYP2C8 GSTM1 CD163 SUCLG2 SDHB ENO3 EHHADH IDH1 FN1 FABP1 APOE GLS2 GSTK1 HPGD MDH2 SERPINF1 SOCS4 AOX1 GSTA3 LEPR GSTA1 IGF2 PTPN11 ACLY LAMP1 ITCH MAN1A1 APOA1 FH CYP4V2 CYP2C9 AGT VEGFB AGTR1 ASS1 C6 LDHA C5 PRAP1 APOB SERPINA1 PDIA4 GPX4 GSTA2 AGXT ADH4 PC TUBA3D P4HB AKR1C3 CYP4F2 VCP APC RHOA MET HJV HSD17B4 HSD17B10 RAF1 H2AC4 ALDH9A1 GDF7 ARG1 SLC27A5 ABATHSP90B1 PTGR1 IL1RAP CRK TDO2 GPX1 PREB PDHA1 BCAP31 C1S G6PC1 CYP4A22 PCK1 TGFB3 LGR5 CYP4F3 ALDH1B1 MOB1A HNF4A CYP2A6 ADH6 SEC61B ITGA1 CYP39A1 RPS27L PXN SESN2 LCAT SAR1B SREBF1 CALR SLC31A1 STAT2 IL17RC CYP2C18 ADSS1 TAOK3 RPTOR SOCS2 PCK2 AMFR RPS11 AKT2 ACAT2 MAP1LC3A SDHD STAT3 MGST3 CCL15 LRP5 SIN3A LEF1 DUSP10 CYP2B6 EFNA1 MAP2K1 HADH SDC1 PLA2G2A RPL39 ACOX3 FRAT1 AIFM1 MLYCD CYP4F12 CD36 SORBS1 IGF1 PDIA6 BCL2A1 SKP1 IFNGR2 GYS2 DNAJA1 ACOX1 OGDHL PDIA3 VAV2 NGF CYP2E1 HSPA5 SLC27A2 GPT2 DNAJC1 ALDH7A1 CDH1 TLE1 PLIN2 MLXIPL CTSZ SEC24A TGFB1 CD40LG H2AC20 OPTN GABARAP DNAJB11 PPID PRKACA

		PDK4 ITGB5 CANX CHMP6 LPIN1 MGST2 MAPK10 TRADD ADCY8 RUVBL1
Alb ^{en} ROI	Decreased	IL2RG PPP2R3A CCL28 MAPK10 GDF6 IL20RA CCDC88C H2AC4 FBXO2 RSPO4 PARD6G SLC25A4 CREB3L4 PLAA HADH RASGRP2 LATS1 ITPR3 PLIN1 DNAJC1 BRD7 CYP7A1 CSNK2A3 NCOR1 GLUL MAP3K5 MBTPS1 PRKACG CPT1C WDR45 RPL26L1 NBR1 PPP2R3B CASP12 CSF1R GPT DVL3 FBN1 PAK2 CEBPA ERN1 TLE1 FMOD MYL7 TNFSF9 IDH3G ATP7B IL18R1 UBB LDHC FGFR2 PPP3CB HSPBP1 EFNA2 CCND3 GDF5 OGDH FGF6 WNT2B GSTM1

Table S7: Partial correlations between genes of dysregulated pathways (MASH vs. NonMASH) in the three distinct ROIs and clinical parameters of MASH. Partial correlation coefficients (r) adjusted by age, sex, and BMI, between the representative genes in the dysregulated pathways and clinical parameters related to MASH and/or hepatic metabolism. Values in parentheses represent FDR values. Bold represents statistically significant (FDR < 0.25).

ROI types	genes	Fibrosis stage (F0-F4)	Steatosis degree (0-3)	Ballooning (0-2)	Lobular inflammation (0-4)	Liver MRI-PDFF (%)	MRE-LSM (kPa)	ELF score	HbA1c (%)	Glucose (mg/dL)	GGT (U/L)	LDL cholesterol (mg/dl)	CK-18 (U/L)	AKR1B10 (pg/mL)
Vin ^{en} ROI	CYP2A6	0.135 (0.629)	0.279 (0.222)	0.307 (0.164)	0.563 (0.012)	0.017 (0.940)	0.117 (0.824)	0.086 (0.785)	-0.049 (0.890)	-0.191 (0.662)	0.151 (0.593)	0.174 (0.479)	0.138 (0.592)	0.247 (0.291)
	ID1	0.214 (0.416)	0.263 (0.244)	0.563 (0.017)	0.328 (0.147)	0.231 (0.491)	0.388 (0.265)	0.396 (0.242)	0.232 (0.460)	0.372 (0.535)	0.465 (0.197)	0.413 (0.279)	0.302 (0.271)	0.525 (0.044)
	EMP3	0.426 (0.104)	0.429 (0.086)	0.446 (0.052)	0.397 (0.088)	0.220 (0.491)	0.489 (0.265)	0.436 (0.178)	0.156 (0.649)	0.077 (0.843)	0.439 (0.197)	0.192 (0.479)	0.254 (0.361)	0.372 (0.136)
	HFE	0.327 (0.248)	0.213 (0.321)	0.435 (0.054)	0.333 (0.147)	0.287 (0.382)	-0.023 (0.993)	0.229 (0.501)	0.510 (0.209)	0.407 (0.535)	0.199 (0.516)	0.235 (0.461)	0.321 (0.271)	0.328 (0.181)
	FBN1	0.246 (0.344)	0.336 (0.144)	0.335 (0.136)	0.317 (0.156)	0.402 (0.252)	0.185 (0.665)	0.338 (0.343)	-0.006 (0.977)	0.062 (0.843)	0.151 (0.593)	0.329 (0.324)	-0.037 (0.865)	0.195 (0.405)
	COL4A2	0.471 (0.076)	0.240 (0.280)	0.517 (0.024)	0.446 (0.051)	0.117 (0.676)	0.167 (0.696)	0.519 (0.178)	0.279 (0.389)	0.300 (0.589)	0.190 (0.519)	0.527 (0.102)	0.332 (0.271)	0.504 (0.044)
	AKT3	0.383 (0.147)	0.212 (0.321)	0.495 (0.029)	0.381 (0.098)	0.121 (0.676)	0.236 (0.581)	0.307 (0.384)	0.388 (0.334)	0.396 (0.535)	0.218 (0.477)	0.361 (0.292)	0.225 (0.426)	0.325 (0.181)
	COL4A1	-0.021 (0.956)	0.517 (0.056)	0.425 (0.054)	0.395 (0.088)	0.402 (0.252)	0.004 (0.993)	0.291 (0.395)	0.303 (0.389)	0.094 (0.827)	0.119 (0.630)	0.224 (0.461)	0.488 (0.151)	0.386 (0.132)
	COL4A6	0.158 (0.575)	0.429 (0.086)	0.260 (0.230)	0.214 (0.316)	0.367 (0.276)	0.400 (0.265)	0.304 (0.384)	0.084 (0.804)	0.100 (0.827)	0.310 (0.270)	0.175 (0.479)	0.140 (0.592)	0.110 (0.617)
	SPARC	0.044 (0.910)	0.457 (0.077)	0.424 (0.054)	0.301 (0.166)	0.314 (0.330)	0.094 (0.836)	0.486 (0.178)	0.407 (0.334)	0.284 (0.589)	0.298 (0.282)	0.303 (0.369)	0.418 (0.211)	0.371 (0.136)
	IL32	0.116 (0.670)	0.621 (0.011)	0.647 (0.005)	0.612 (0.007)	0.363 (0.276)	0.252 (0.561)	0.441 (0.178)	0.257 (0.413)	0.068 (0.843)	0.377 (0.246)	0.445 (0.245)	0.654 (0.013)	0.653 (0.010)
	CCL21	0.504 (0.060)	0.423 (0.086)	0.544 (0.019)	0.602 (0.007)	0.190 (0.508)	0.368 (0.265)	0.473 (0.178)	0.081 (0.804)	0.004 (0.987)	0.340 (0.270)	0.350 (0.292)	0.393 (0.212)	0.533 (0.044)
	ACKR3	0.631 (0.024)	0.319 (0.160)	0.512 (0.024)	0.507 (0.026)	0.150 (0.619)	0.136 (0.789)	0.267 (0.441)	0.341 (0.368)	0.181 (0.663)	0.324 (0.270)	0.189 (0.479)	0.214 (0.439)	0.477 (0.053)
	CXCL12	0.582 (0.026)	0.482 (0.061)	0.483 (0.032)	0.502 (0.026)	0.202 (0.495)	0.367 (0.265)	0.464 (0.178)	0.036 (0.902)	-0.103 (0.827)	0.314 (0.270)	0.111 (0.657)	0.096 (0.696)	0.508 (0.044)
	S100A9	0.289 (0.268)	0.378 (0.107)	0.291 (0.182)	0.664 (0.007)	0.061 (0.851)	-0.101 (0.836)	-0.109 (0.785)	-0.088 (0.804)	-0.337 (0.535)	0.017 (0.937)	0.228 (0.461)	0.138 (0.592)	0.298 (0.219)
	GRK5	0.288 (0.268)	0.342 (0.144)	0.396 (0.072)	0.610 (0.007)	0.259 (0.449)	-0.005 (0.993)	0.092 (0.785)	-0.166 (0.644)	-0.356 (0.535)	0.082 (0.731)	0.220 (0.461)	0.390 (0.212)	0.518 (0.044)
	VASP	0.563 (0.026)	0.335 (0.144)	0.549 (0.019)	0.604 (0.007)	-0.033 (0.916)	0.451 (0.265)	0.207 (0.501)	0.102 (0.804)	0.022 (0.958)	0.423 (0.197)	0.294 (0.369)	0.310 (0.271)	0.464 (0.058)
	ZYX	0.268 (0.303)	0.390 (0.100)	0.537 (0.019)	0.578 (0.010)	0.221 (0.491)	-0.008 (0.993)	0.013 (0.955)	0.483 (0.209)	0.160 (0.711)	0.137 (0.593)	0.172 (0.479)	0.463 (0.151)	0.276 (0.254)

CD45 ^{en} ROI	<i>GPT2</i>	-0.290 (0.268)	-0.419 (0.086)	-0.577 (0.016)	-0.486 (0.031)	-0.202 (0.495)	-0.402 (0.265)	-0.213 (0.501)	-0.279 (0.389)	-0.109 (0.827)	-0.323 (0.270)	-0.073 (0.733)	-0.304 (0.271)	-0.353 (0.154)
	<i>GLUL</i>	-0.570 (0.026)	-0.410 (0.090)	-0.429 (0.054)	-0.348 (0.132)	-0.337 (0.322)	-0.351 (0.279)	-0.225 (0.501)	-0.254 (0.413)	-0.192 (0.662)	-0.374 (0.246)	-0.085 (0.722)	-0.092 (0.696)	-0.401 (0.121)
	<i>CYP3A4</i>	-0.468 (0.076)	-0.509 (0.056)	-0.690 (0.003)	-0.518 (0.024)	-0.410 (0.252)	-0.418 (0.265)	-0.205 (0.501)	-0.311 (0.389)	-0.219 (0.662)	-0.425 (0.197)	-0.235 (0.461)	-0.284 (0.297)	-0.484 (0.053)
	<i>CYP1A2</i>	-0.419 (0.104)	-0.490 (0.061)	-0.686 (0.003)	-0.625 (0.007)	-0.397 (0.252)	-0.264 (0.558)	-0.159 (0.629)	-0.373 (0.334)	-0.278 (0.589)	-0.427 (0.197)	-0.380 (0.292)	-0.368 (0.213)	-0.651 (0.010)
	<i>CYP2C19</i>	-0.421 (0.104)	-0.651 (0.011)	-0.599 (0.012)	-0.599 (0.007)	-0.619 (0.038)	-0.189 (0.665)	-0.384 (0.242)	-0.364 (0.334)	-0.230 (0.662)	-0.251 (0.396)	-0.548 (0.102)	-0.459 (0.151)	-0.595 (0.023)
	<i>RAC3</i>	0.012 (0.956)	-0.617 (0.011)	-0.327 (0.142)	-0.255 (0.239)	-0.590 (0.038)	-0.205 (0.665)	0.014 (0.955)	-0.176 (0.643)	-0.211 (0.662)	-0.366 (0.246)	-0.215 (0.461)	-0.173 (0.552)	-0.270 (0.254)
	<i>GNG3</i>	0.296 (0.268)	-0.402 (0.092)	-0.247 (0.245)	-0.309 (0.161)	-0.322 (0.330)	-0.002 (0.993)	-0.080 (0.785)	-0.290 (0.389)	-0.213 (0.662)	-0.141 (0.593)	-0.364 (0.292)	-0.373 (0.213)	-0.125 (0.592)
	<i>COL4A1</i>	0.419 (0.130)	0.294 (0.193)	0.527 (0.016)	0.304 (0.236)	0.263 (0.352)	0.314 (0.180)	0.477 (0.065)	0.423 (0.195)	0.446 (0.274)	0.427 (0.078)	0.393 (0.319)	0.414 (0.213)	0.437 (0.154)
	<i>CCL2</i>	0.397 (0.152)	0.370 (0.111)	0.372 (0.080)	0.287 (0.236)	0.415 (0.185)	0.128 (0.636)	0.193 (0.406)	0.377 (0.195)	0.398 (0.274)	0.160 (0.494)	0.451 (0.226)	0.094 (0.663)	0.095 (0.695)
	<i>IL32</i>	0.476 (0.078)	0.560 (0.022)	0.596 (0.007)	0.379 (0.169)	0.537 (0.088)	0.501 (0.057)	0.311 (0.199)	0.388 (0.195)	0.301 (0.393)	0.668 (0.009)	0.197 (0.516)	0.262 (0.385)	0.316 (0.221)
	<i>LTB</i>	0.087 (0.687)	0.333 (0.147)	0.385 (0.072)	0.268 (0.241)	0.351 (0.266)	0.011 (0.960)	0.319 (0.194)	0.076 (0.802)	0.148 (0.722)	0.117 (0.609)	0.174 (0.521)	0.177 (0.569)	0.515 (0.099)
	<i>LYZ</i>	0.260 (0.323)	0.266 (0.237)	0.657 (0.004)	0.341 (0.214)	0.045 (0.837)	0.455 (0.073)	0.585 (0.026)	0.356 (0.219)	0.298 (0.393)	0.455 (0.064)	0.074 (0.763)	0.378 (0.213)	0.539 (0.099)
	<i>CD74</i>	0.585 (0.033)	0.515 (0.028)	0.644 (0.004)	0.465 (0.110)	0.312 (0.284)	0.554 (0.038)	0.601 (0.026)	0.213 (0.507)	0.236 (0.447)	0.504 (0.043)	0.368 (0.319)	0.300 (0.320)	0.398 (0.166)
	<i>CD68</i>	0.539 (0.033)	0.454 (0.046)	0.633 (0.004)	0.452 (0.111)	0.204 (0.430)	0.604 (0.029)	0.595 (0.026)	0.550 (0.134)	0.362 (0.274)	0.578 (0.039)	0.331 (0.409)	0.519 (0.116)	0.417 (0.163)
	<i>IGHG1</i>	0.544 (0.033)	0.251 (0.258)	0.617 (0.005)	0.424 (0.133)	0.176 (0.458)	0.306 (0.185)	0.461 (0.065)	0.271 (0.358)	0.237 (0.447)	0.335 (0.144)	0.233 (0.516)	0.240 (0.432)	0.259 (0.306)
	<i>IGKC</i>	0.550 (0.033)	0.193 (0.366)	0.566 (0.010)	0.177 (0.408)	0.123 (0.598)	0.432 (0.077)	0.521 (0.054)	0.458 (0.195)	0.536 (0.172)	0.330 (0.144)	0.298 (0.492)	0.160 (0.569)	0.063 (0.774)
	<i>RPL31</i>	0.423 (0.130)	0.524 (0.027)	0.631 (0.004)	0.471 (0.110)	0.244 (0.368)	0.490 (0.057)	0.496 (0.061)	0.142 (0.603)	0.117 (0.737)	0.460 (0.064)	0.180 (0.521)	0.322 (0.285)	0.410 (0.163)
	<i>RPS19</i>	0.382 (0.160)	0.490 (0.031)	0.505 (0.021)	0.360 (0.191)	0.302 (0.285)	0.380 (0.115)	0.382 (0.117)	0.185 (0.568)	0.116 (0.737)	0.364 (0.119)	0.034 (0.873)	0.287 (0.333)	0.350 (0.208)
	<i>RPS13</i>	0.261 (0.323)	0.444 (0.050)	0.419 (0.054)	0.291 (0.236)	0.345 (0.266)	0.401 (0.103)	0.451 (0.065)	0.023 (0.949)	0.122 (0.737)	0.322 (0.148)	0.264 (0.516)	0.144 (0.569)	0.228 (0.368)
	<i>RPLP1</i>	0.251 (0.330)	0.501 (0.030)	0.407 (0.060)	0.234 (0.281)	0.522 (0.088)	0.339 (0.158)	0.375 (0.119)	0.210 (0.507)	0.279 (0.424)	0.395 (0.100)	0.383 (0.319)	0.159 (0.569)	0.195 (0.423)
	<i>RPL37</i>	0.368 (0.160)	0.339 (0.146)	0.361 (0.086)	0.273 (0.241)	0.242 (0.368)	0.431 (0.077)	0.448 (0.065)	-0.014 (0.949)	0.034 (0.952)	0.337 (0.144)	0.191 (0.516)	0.150 (0.569)	0.209 (0.402)
	<i>CTSD</i>	0.360 (0.162)	0.498 (0.030)	0.489 (0.025)	0.264 (0.241)	0.364 (0.266)	0.503 (0.057)	0.448 (0.065)	0.376 (0.195)	0.185 (0.605)	0.524 (0.043)	-0.088 (0.741)	0.368 (0.213)	0.344 (0.208)
	<i>ATG13</i>	0.112 (0.627)	0.545 (0.022)	0.385 (0.072)	0.515 (0.083)	0.335 (0.269)	-0.016 (0.960)	-0.120 (0.596)	0.072 (0.802)	-0.010 (0.964)	0.193 (0.415)	0.129 (0.652)	0.114 (0.621)	0.359 (0.208)
	<i>HSPA8</i>	0.226 (0.359)	0.463 (0.044)	0.666 (0.004)	0.331 (0.220)	0.295 (0.285)	0.467 (0.068)	0.419 (0.085)	0.400 (0.195)	0.364 (0.274)	0.448 (0.064)	0.217 (0.516)	0.428 (0.213)	0.454 (0.154)

Alb ^{en} ROI	<i>FTH1</i>	0.298 (0.262)	0.590 (0.016)	0.297 (0.158)	0.298 (0.236)	0.545 (0.088)	0.356 (0.140)	0.196 (0.406)	0.161 (0.593)	0.087 (0.808)	0.419 (0.080)	0.200 (0.516)	0.171 (0.569)	0.153 (0.528)
	<i>ITGB1</i>	0.194 (0.432)	0.543 (0.022)	0.567 (0.010)	0.284 (0.236)	0.421 (0.185)	0.487 (0.057)	0.416 (0.085)	0.421 (0.195)	0.409 (0.274)	0.507 (0.043)	0.191 (0.516)	0.329 (0.285)	0.446 (0.154)
	<i>VIM</i>	0.546 (0.033)	0.297 (0.193)	0.561 (0.010)	0.252 (0.255)	0.219 (0.415)	0.433 (0.077)	0.586 (0.026)	0.281 (0.358)	0.356 (0.274)	0.385 (0.100)	0.192 (0.516)	0.122 (0.620)	0.298 (0.233)
	<i>CTSS</i>	0.121 (0.623)	0.588 (0.016)	0.468 (0.033)	0.417 (0.133)	0.487 (0.116)	0.382 (0.115)	0.494 (0.061)	0.278 (0.358)	0.239 (0.447)	0.384 (0.100)	0.541 (0.093)	0.399 (0.213)	0.329 (0.210)
	<i>C1QC</i>	0.333 (0.200)	0.588 (0.016)	0.532 (0.015)	0.523 (0.083)	0.321 (0.282)	0.621 (0.029)	0.461 (0.065)	0.163 (0.593)	0.019 (0.964)	0.531 (0.043)	0.265 (0.516)	0.482 (0.143)	0.359 (0.208)
	<i>C1QB</i>	0.130 (0.620)	0.432 (0.055)	0.459 (0.035)	0.289 (0.236)	0.193 (0.430)	0.558 (0.038)	0.258 (0.280)	0.280 (0.358)	0.260 (0.447)	0.543 (0.043)	0.092 (0.741)	0.162 (0.569)	0.308 (0.225)
	<i>CYP2C19</i>	-0.226 (0.359)	-0.202 (0.358)	-0.424 (0.054)	-0.392 (0.162)	-0.194 (0.430)	0.071 (0.814)	-0.294 (0.219)	-0.153 (0.593)	-0.080 (0.808)	0.038 (0.861)	-0.248 (0.516)	-0.383 (0.213)	-0.336 (0.208)
	<i>CREB3</i>	-0.374 (0.160)	-0.750 (0.001)	-0.662 (0.004)	-0.530 (0.083)	-0.410 (0.185)	-0.328 (0.166)	-0.546 (0.043)	-0.492 (0.184)	-0.396 (0.274)	-0.451 (0.064)	-0.532 (0.093)	-0.613 (0.036)	-0.516 (0.099)
	<i>LDLR</i>	0.466 (0.144)	0.416 (0.108)	0.232 (0.300)	0.429 (0.098)	0.320 (0.189)	-0.155 (0.751)	-0.012 (0.959)	0.108 (0.771)	-0.151 (0.867)	0.085 (0.912)	0.159 (0.592)	0.358 (0.359)	0.294 (0.286)
	<i>INHBC</i>	0.170 (0.708)	0.355 (0.134)	0.447 (0.256)	0.361 (0.125)	0.240 (0.330)	0.254 (0.706)	0.133 (0.834)	0.112 (0.771)	0.138 (0.867)	0.519 (0.136)	0.209 (0.547)	0.277 (0.593)	0.367 (0.212)
	<i>ICAM1</i>	0.462 (0.144)	0.352 (0.134)	0.364 (0.256)	0.556 (0.034)	0.076 (0.729)	-0.036 (0.908)	0.258 (0.834)	0.068 (0.832)	-0.244 (0.833)	0.011 (0.960)	0.221 (0.547)	0.547 (0.070)	0.308 (0.273)
	<i>PLCD1</i>	0.413 (0.205)	0.197 (0.357)	0.393 (0.256)	0.416 (0.098)	0.094 (0.697)	0.481 (0.501)	0.397 (0.834)	-0.029 (0.892)	-0.067 (0.888)	0.355 (0.272)	0.155 (0.592)	-0.010 (0.964)	0.314 (0.273)
	<i>IL32</i>	0.554 (0.124)	0.687 (0.005)	0.713 (0.002)	0.735 (0.001)	0.339 (0.177)	0.230 (0.706)	0.253 (0.834)	0.227 (0.511)	-0.030 (0.888)	0.510 (0.136)	0.282 (0.547)	0.638 (0.020)	0.601 (0.031)
	<i>TNFRSF4</i>	0.301 (0.365)	0.447 (0.102)	0.321 (0.256)	0.286 (0.200)	0.435 (0.106)	0.131 (0.766)	0.220 (0.834)	0.252 (0.511)	0.049 (0.888)	-0.020 (0.960)	0.092 (0.728)	0.169 (0.679)	0.259 (0.322)
	<i>SQSTM1</i>	0.308 (0.365)	0.307 (0.166)	0.274 (0.270)	0.522 (0.037)	0.184 (0.436)	-0.133 (0.766)	-0.202 (0.834)	-0.264 (0.511)	-0.477 (0.458)	0.027 (0.960)	0.097 (0.728)	0.170 (0.679)	0.160 (0.466)
	<i>CRK</i>	0.513 (0.129)	0.511 (0.054)	0.381 (0.256)	0.359 (0.125)	0.555 (0.047)	0.368 (0.670)	0.257 (0.834)	0.201 (0.577)	0.178 (0.867)	0.465 (0.185)	0.272 (0.547)	0.140 (0.679)	0.410 (0.171)
	<i>TNFAIP3</i>	0.406 (0.205)	0.347 (0.134)	0.298 (0.256)	0.522 (0.037)	0.218 (0.361)	-0.205 (0.706)	-0.072 (0.853)	0.064 (0.832)	-0.244 (0.833)	-0.020 (0.960)	0.093 (0.728)	0.139 (0.679)	0.396 (0.171)
	<i>SLC25A4</i>	0.005 (0.983)	0.646 (0.008)	0.217 (0.321)	0.324 (0.161)	0.611 (0.047)	0.322 (0.670)	0.268 (0.834)	-0.043 (0.876)	-0.057 (0.888)	0.354 (0.272)	0.349 (0.547)	0.283 (0.593)	0.232 (0.358)
	<i>FABP4</i>	0.320 (0.365)	0.422 (0.108)	0.315 (0.256)	0.263 (0.233)	0.559 (0.047)	-0.193 (0.706)	0.278 (0.834)	0.228 (0.511)	0.045 (0.888)	-0.048 (0.960)	0.256 (0.547)	0.444 (0.248)	0.220 (0.373)
	<i>PRICKLE4</i>	0.116 (0.775)	0.424 (0.108)	0.336 (0.256)	0.363 (0.125)	0.353 (0.164)	0.092 (0.768)	0.019 (0.959)	0.312 (0.511)	0.187 (0.867)	0.272 (0.451)	0.172 (0.592)	0.141 (0.679)	0.404 (0.171)
	<i>AGXT</i>	-0.097 (0.775)	-0.401 (0.115)	-0.171 (0.425)	-0.361 (0.125)	-0.542 (0.047)	-0.016 (0.941)	-0.127 (0.834)	-0.272 (0.511)	-0.049 (0.888)	-0.128 (0.822)	-0.166 (0.592)	-0.225 (0.679)	-0.446 (0.171)
	<i>GLS2</i>	-0.286 (0.365)	-0.243 (0.275)	-0.287 (0.256)	-0.254 (0.240)	-0.444 (0.106)	-0.110 (0.768)	0.086 (0.836)	-0.283 (0.511)	-0.144 (0.867)	-0.125 (0.822)	-0.154 (0.592)	-0.140 (0.679)	-0.165 (0.466)
	<i>PCK1</i>	-0.062 (0.842)	-0.311 (0.166)	-0.299 (0.256)	-0.249 (0.241)	-0.412 (0.112)	-0.411 (0.644)	-0.250 (0.834)	-0.098 (0.771)	-0.035 (0.888)	-0.346 (0.272)	-0.058 (0.822)	-0.168 (0.679)	-0.469 (0.171)
	<i>IFNA2</i>	-0.270 (0.389)	-0.378 (0.125)	-0.337 (0.256)	-0.594 (0.028)	-0.236 (0.330)	-0.328 (0.670)	-0.101 (0.834)	0.319 (0.511)	0.380 (0.833)	-0.406 (0.272)	-0.231 (0.547)	-0.200 (0.679)	-0.261 (0.322)

<i>RPL6</i>	-0.106 (0.775)	-0.306 (0.166)	-0.259 (0.276)	-0.345 (0.137)	-0.400 (0.112)	-0.185 (0.706)	-0.097 (0.834)	-0.267 (0.511)	-0.236 (0.833)	-0.102 (0.883)	-0.410 (0.402)	-0.026 (0.940)	-0.288 (0.286)
<i>RPL34</i>	-0.108 (0.775)	-0.397 (0.115)	-0.241 (0.291)	-0.313 (0.170)	-0.467 (0.088)	-0.203 (0.706)	-0.128 (0.834)	-0.351 (0.511)	-0.244 (0.833)	-0.170 (0.710)	-0.251 (0.547)	-0.120 (0.715)	-0.336 (0.262)
<i>RPL10A</i>	-0.102 (0.775)	-0.528 (0.050)	-0.339 (0.256)	-0.383 (0.125)	-0.483 (0.081)	-0.282 (0.685)	-0.184 (0.834)	-0.443 (0.511)	-0.285 (0.833)	-0.310 (0.352)	-0.268 (0.547)	-0.223 (0.679)	-0.329 (0.262)
<i>RPL38</i>	-0.332 (0.365)	-0.549 (0.045)	-0.400 (0.256)	-0.548 (0.034)	-0.502 (0.074)	-0.237 (0.706)	-0.175 (0.834)	-0.191 (0.582)	-0.087 (0.888)	-0.255 (0.476)	-0.451 (0.402)	-0.143 (0.679)	-0.204 (0.399)
<i>IGF2</i>	-0.179 (0.708)	-0.327 (0.156)	-0.263 (0.276)	-0.423 (0.098)	-0.408 (0.112)	-0.175 (0.706)	-0.174 (0.834)	-0.335 (0.511)	-0.188 (0.867)	-0.173 (0.710)	-0.407 (0.402)	-0.370 (0.359)	-0.438 (0.171)
<i>CHUK</i>	-0.078 (0.815)	-0.472 (0.083)	-0.289 (0.256)	-0.418 (0.098)	-0.372 (0.144)	-0.095 (0.768)	-0.111 (0.834)	0.122 (0.771)	0.073 (0.888)	-0.372 (0.272)	-0.209 (0.547)	-0.394 (0.354)	-0.727 (0.002)
<i>G6PC1</i>	-0.161 (0.708)	-0.352 (0.134)	-0.253 (0.277)	-0.303 (0.179)	-0.407 (0.112)	-0.300 (0.685)	-0.117 (0.834)	-0.244 (0.511)	-0.056 (0.888)	-0.355 (0.272)	-0.006 (0.978)	-0.088 (0.743)	-0.408 (0.171)
<i>COX6A2</i>	-0.035 (0.909)	-0.376 (0.125)	-0.372 (0.256)	-0.467 (0.077)	-0.299 (0.217)	0.041 (0.908)	0.032 (0.959)	0.151 (0.709)	0.172 (0.867)	0.011 (0.960)	-0.218 (0.547)	-0.113 (0.715)	-0.253 (0.322)
<i>SDHC</i>	-0.290 (0.365)	-0.230 (0.292)	-0.324 (0.256)	-0.363 (0.125)	-0.333 (0.177)	-0.121 (0.768)	0.178 (0.834)	-0.379 (0.511)	-0.293 (0.833)	-0.197 (0.686)	-0.276 (0.547)	0.103 (0.716)	-0.195 (0.405)

Table S8: Partial correlations between genes of dysregulated pathways (MASH-HF vs. MASH-LF) in the three distinct ROIs and clinical parameters of fibrosis. Partial correlation coefficients (r) adjusted by age, sex, and BMI, between the representative genes in the dysregulated pathways and clinical parameters for diagnosis of fibrosis. Values in parentheses represent FDR values. Bold represents FDR < 0.25.

ROI types	Gene symbol	Fibrosis stage (F0-F4)	MRE-LSM (kPa)	ELF score	CK-18 (U/L)	AKR1B10 (pg/mL)
Vin ^{en} ROI	<i>MAPK8</i>	0.679 (0.013)	0.062 (0.983)	0.080 (0.804)	-0.002 (0.994)	-0.050 (0.918)
	<i>MAP3K14</i>	0.662 (0.015)	-0.025 (0.983)	0.112 (0.765)	-0.008 (0.994)	-0.142 (0.918)
	<i>NOS1</i>	0.737 (0.008)	0.078 (0.983)	0.165 (0.765)	-0.235 (0.994)	-0.033 (0.918)
	<i>CCL3L3</i>	0.700 (0.011)	0.382 (0.983)	0.272 (0.765)	-0.259 (0.994)	0.181 (0.918)
	<i>GNG3</i>	0.772 (0.007)	0.172 (0.983)	0.199 (0.765)	-0.027 (0.994)	0.311 (0.918)
	<i>CYP11B2</i>	0.712 (0.010)	0.225 (0.983)	0.440 (0.765)	-0.150 (0.994)	-0.112 (0.918)
	<i>ACVR1C</i>	0.842 (0.007)	0.395 (0.983)	0.354 (0.765)	0.083 (0.994)	-0.034 (0.918)
	<i>TNXB</i>	0.473 (0.102)	-0.170 (0.983)	0.176 (0.765)	-0.091 (0.994)	0.194 (0.918)
	<i>NPNT</i>	0.594 (0.034)	0.283 (0.983)	0.283 (0.765)	-0.129 (0.994)	0.120 (0.918)
	<i>PPP1R12A</i>	0.758 (0.007)	0.255 (0.983)	0.283 (0.765)	-0.012 (0.994)	0.058 (0.918)
	<i>WNT8A</i>	0.809 (0.007)	0.386 (0.983)	0.319 (0.765)	-0.117 (0.994)	0.094 (0.918)
	<i>WNT8B</i>	0.659 (0.016)	0.230 (0.983)	0.582 (0.765)	0.058 (0.994)	0.083 (0.918)
	<i>COX6A2</i>	0.824 (0.007)	0.477 (0.983)	0.327 (0.765)	0.166 (0.994)	0.268 (0.918)
	<i>AGXT</i>	-0.777 (0.007)	-0.039 (0.983)	-0.138 (0.765)	0.152 (0.994)	0.150 (0.918)
	<i>APOC1</i>	-0.745 (0.008)	-0.022 (0.983)	-0.132 (0.765)	0.219 (0.994)	0.272 (0.918)
	<i>APOH</i>	-0.695 (0.011)	0.037 (0.983)	-0.117 (0.765)	0.200 (0.994)	0.329 (0.918)
	<i>APOA1</i>	-0.714 (0.010)	-0.014 (0.983)	-0.181 (0.765)	0.193 (0.994)	0.285 (0.918)
	<i>APOC3</i>	-0.755 (0.007)	-0.040 (0.983)	-0.145 (0.765)	0.164 (0.994)	0.298 (0.918)
	<i>APOE</i>	-0.730 (0.009)	-0.033 (0.983)	-0.224 (0.765)	0.159 (0.994)	0.187 (0.918)
	<i>C3</i>	-0.760 (0.007)	-0.048 (0.983)	-0.120 (0.765)	0.232 (0.994)	0.313 (0.918)
	<i>VTN</i>	-0.706 (0.010)	0.022 (0.983)	-0.219 (0.765)	0.138 (0.994)	0.313 (0.918)
	<i>ALDH2</i>	-0.738 (0.008)	-0.044 (0.983)	-0.388 (0.765)	0.039 (0.994)	0.157 (0.918)
	<i>ADH1B</i>	-0.772 (0.007)	-0.020 (0.983)	-0.195 (0.765)	0.130 (0.994)	0.158 (0.918)

	<i>TF</i>	-0.713 (0.010)	0.007 (0.983)	-0.196 (0.765)	0.093 (0.994)	0.269 (0.918)
	<i>ALDOB</i>	-0.793 (0.007)	-0.064 (0.983)	-0.109 (0.765)	0.216 (0.994)	0.258 (0.918)
	<i>GSTM1</i>	-0.684 (0.012)	-0.506 (0.983)	-0.383 (0.765)	0.192 (0.994)	-0.263 (0.918)
CD45 ^{en} ROI	<i>XCL1</i>	0.379 (0.149)	0.331 (0.920)	0.279 (0.586)	0.045 (0.994)	0.110 (0.847)
	<i>GDF1</i>	0.368 (0.149)	-0.066 (0.946)	0.079 (0.786)	-0.018 (0.994)	0.109 (0.847)
	<i>TNFRSF13C</i>	0.195 (0.377)	-0.214 (0.920)	-0.199 (0.586)	-0.025 (0.994)	-0.406 (0.826)
	<i>RELT</i>	0.429 (0.149)	0.044 (0.946)	0.170 (0.586)	0.307 (0.994)	0.006 (0.991)
	<i>AMHR2</i>	0.411 (0.149)	0.042 (0.946)	0.341 (0.586)	0.272 (0.994)	0.393 (0.826)
	<i>TNFRSF13B</i>	0.361 (0.149)	-0.091 (0.946)	0.125 (0.687)	-0.145 (0.994)	0.101 (0.847)
	<i>DNAJB1</i>	0.607 (0.044)	-0.054 (0.946)	0.129 (0.687)	0.119 (0.994)	-0.053 (0.877)
	<i>LPAR2</i>	0.418 (0.149)	0.033 (0.946)	-0.027 (0.905)	0.012 (0.994)	-0.099 (0.847)
	<i>WNT8A</i>	0.394 (0.149)	-0.171 (0.920)	0.027 (0.905)	-0.037 (0.994)	0.148 (0.847)
	<i>APC2</i>	0.270 (0.240)	0.024 (0.946)	0.249 (0.586)	-0.047 (0.994)	0.166 (0.847)
	<i>PPP2R2A</i>	0.402 (0.149)	0.243 (0.920)	0.172 (0.586)	-0.001 (0.996)	0.128 (0.847)
	<i>S100A6</i>	0.495 (0.149)	0.150 (0.920)	0.425 (0.586)	0.152 (0.994)	0.220 (0.847)
	<i>RASGRP4</i>	0.021 (0.923)	-0.134 (0.920)	0.084 (0.786)	-0.029 (0.994)	-0.224 (0.847)
	<i>APOC1</i>	-0.323 (0.176)	0.165 (0.920)	-0.258 (0.586)	-0.135 (0.994)	-0.185 (0.847)
	<i>APOC3</i>	-0.358 (0.149)	0.086 (0.946)	-0.331 (0.586)	-0.090 (0.994)	-0.086 (0.847)
	<i>APOC2</i>	-0.315 (0.176)	0.204 (0.920)	-0.170 (0.586)	0.063 (0.994)	-0.002 (0.991)
	<i>APOE</i>	-0.218 (0.331)	0.229 (0.920)	-0.209 (0.586)	-0.130 (0.994)	-0.093 (0.847)
	<i>APOA1</i>	-0.282 (0.226)	0.171 (0.920)	-0.244 (0.586)	-0.106 (0.994)	-0.098 (0.847)
	<i>APOH</i>	-0.375 (0.149)	0.167 (0.920)	-0.206 (0.586)	-0.239 (0.994)	-0.185 (0.847)
	<i>C3</i>	-0.360 (0.149)	0.153 (0.920)	-0.186 (0.586)	-0.209 (0.994)	-0.184 (0.847)
	<i>VTN</i>	-0.259 (0.251)	0.234 (0.920)	-0.169 (0.586)	-0.216 (0.994)	-0.070 (0.850)
	<i>ACAT1</i>	-0.314 (0.176)	0.178 (0.920)	-0.290 (0.586)	-0.141 (0.994)	-0.148 (0.847)
	<i>TF</i>	-0.332 (0.172)	0.206 (0.920)	-0.213 (0.586)	-0.209 (0.994)	-0.080 (0.847)
	<i>ALDOB</i>	-0.421 (0.149)	-0.015 (0.946)	-0.319 (0.586)	-0.123 (0.994)	-0.157 (0.847)
	<i>GSTA1</i>	-0.349 (0.153)	0.126 (0.920)	-0.298 (0.586)	-0.013 (0.994)	-0.151 (0.847)

	<i>HPD</i>	-0.385 (0.149)	0.095 (0.946)	-0.291 (0.586)	-0.221 (0.994)	-0.160 (0.847)
Alb ^{en} ROI	<i>COL1A2</i>	0.606 (0.058)	0.171 (0.927)	0.217 (0.966)	-0.007 (0.982)	-0.062 (0.955)
	<i>CAPN2</i>	0.352 (0.279)	-0.091 (0.927)	0.169 (0.966)	-0.100 (0.955)	0.149 (0.791)
	<i>ELMO1</i>	0.659 (0.043)	0.165 (0.927)	0.191 (0.966)	0.302 (0.955)	0.406 (0.791)
	<i>CCL3L3</i>	0.707 (0.043)	0.129 (0.927)	0.175 (0.966)	0.136 (0.955)	-0.027 (0.962)
	<i>NPC1</i>	0.262 (0.402)	-0.152 (0.927)	-0.064 (0.966)	-0.170 (0.955)	-0.528 (0.791)
	<i>C7</i>	0.644 (0.043)	0.227 (0.927)	0.234 (0.966)	-0.195 (0.955)	-0.221 (0.791)
	<i>IFNA14</i>	0.296 (0.360)	0.070 (0.927)	0.125 (0.966)	0.088 (0.955)	0.456 (0.791)
	<i>SGK1</i>	0.638 (0.043)	-0.152 (0.927)	-0.092 (0.966)	-0.058 (0.955)	-0.420 (0.791)
	<i>PPP2R5E</i>	0.388 (0.233)	-0.033 (0.954)	0.421 (0.966)	0.233 (0.955)	0.078 (0.949)
	<i>WNT8A</i>	0.589 (0.058)	0.127 (0.927)	0.240 (0.966)	0.174 (0.955)	0.318 (0.791)
	<i>CD79B</i>	0.653 (0.043)	0.208 (0.927)	0.134 (0.966)	0.036 (0.955)	0.242 (0.791)
	<i>KLF16</i>	0.666 (0.043)	-0.097 (0.927)	0.045 (0.966)	0.289 (0.955)	0.310 (0.791)
	<i>CHMP1A</i>	0.418 (0.199)	0.243 (0.927)	0.076 (0.966)	-0.070 (0.955)	-0.203 (0.791)
	<i>GPT</i>	-0.540 (0.081)	0.068 (0.927)	-0.194 (0.966)	-0.580 (0.775)	-0.397 (0.791)
	<i>PRKACG</i>	-0.595 (0.058)	-0.440 (0.927)	-0.379 (0.966)	-0.103 (0.955)	-0.274 (0.791)
	<i>ATP7A</i>	-0.292 (0.360)	0.077 (0.927)	0.018 (0.992)	-0.165 (0.955)	0.160 (0.791)
	<i>CSF1R</i>	-0.556 (0.073)	0.161 (0.927)	-0.043 (0.966)	0.266 (0.955)	0.175 (0.791)
	<i>GDF5</i>	-0.675 (0.043)	-0.201 (0.927)	0.180 (0.966)	0.235 (0.955)	0.015 (0.962)
	<i>HSPBP1</i>	-0.568 (0.068)	0.018 (0.954)	0.119 (0.966)	0.235 (0.955)	0.200 (0.791)
	<i>CREB3L4</i>	-0.820 (0.016)	-0.115 (0.927)	-0.362 (0.966)	-0.402 (0.955)	-0.316 (0.791)
	<i>WNT2B</i>	-0.597 (0.058)	-0.226 (0.927)	-0.332 (0.966)	-0.169 (0.955)	0.153 (0.791)
	<i>GSTM1</i>	-0.518 (0.094)	-0.216 (0.927)	-0.001 (0.999)	0.348 (0.955)	-0.259 (0.791)
	<i>PIAS4</i>	-0.694 (0.043)	-0.427 (0.927)	-0.208 (0.966)	0.073 (0.955)	-0.277 (0.791)
	<i>EFNA2</i>	-0.637 (0.043)	-0.210 (0.927)	-0.249 (0.966)	-0.062 (0.955)	0.189 (0.791)
	<i>FGF6</i>	-0.696 (0.043)	0.027 (0.954)	-0.059 (0.966)	-0.031 (0.955)	0.044 (0.962)
	<i>PPP3CB</i>	-0.645 (0.043)	0.168 (0.927)	0.120 (0.966)	0.193 (0.955)	0.356 (0.791)

Method S1

Participants

For spatial transcriptomics analysis, we selected 24 patients from three parent cohort studies on metabolic dysfunction-associated steatotic liver diseases (MASLD) in the Gachon University Gil Medical Center (GMC) who had formalin-fixed paraffin-embedded (FFPE) liver tissue samples, clinical information, and disease-specific assessment data related to MASLD. The study subjects were selected based on the presence or absence of metabolic dysfunction-associated steatohepatitis (MASH) and the degree of fibrosis progression. The study subjects included individuals who underwent bariatric surgery (BS), those who had a liver biopsy for MASLD, or liver transplant donors. MASLD was evaluated before surgery, and liver tissue biopsies were taken during the procedure. The primary objective of this study was to investigate the spatial transcriptomic profile of MASH. MASH was defined based on histological findings, specifically a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 4 or higher, with a subscore of at least 1 for each of the following subcomponents: steatosis, hepatocyte ballooning, and lobular inflammation. The age range for the inclusion criteria for parent studies was from 19 to 70 years. Among 18 participants with bulk RNA sequencing (RNA-Seq) data, four patients had their FFPE liver tissues subjected to the GeoMx digital spatial profiler (DSP) RNA assay.

Liver tissue sampling and preparation

Liver biopsy and tissue sampling procedures were conducted during BS, living donor hepatectomy for living liver transplantation, and percutaneous liver biopsy procedures in cases of abnormal liver function. A small portion of the biopsy samples were stored frozen, while the remaining part was fixed in 4% buffered neutral formalin (pH 7.4), processed, and paraffin-embedded for histological assessment. Paraffin-embedded 5 μ m sections of liver biopsy samples were stained with hematoxylin and eosin and Masson's trichrome. Histological scoring, including NAS and fibrosis staging, was performed

utilizing the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network histologic scoring system, as outlined by Kleiner (18). For the histological scoring, an expert pathologist evaluated the stained specimens without knowledge of the patients' clinical and radiologic findings. Furthermore, a portion of each liver tissue was rapidly frozen in liquid nitrogen and stored at -80°C until further analysis.

Human liver spatial RNA profiling using GeoMx DSP

Spatial transcriptomic profiling was performed using the GeoMx Human Whole Transcriptome Atlas panel. Libraries were prepared following the guidelines provided in the NanoString GeoMx Library Preparation Manual and pooled to achieve an equimolar concentration. RNA-Seq was performed on an Illumina NovaSeq 6000 platform under standard conditions, with a sequencing depth of 30 read pairs/ μm^2 .

In R (Version 4.2.2), quality control and pre-processing were conducted using the "GeoMxTools" package (Version 3.2.0) and the "GeoMxWorkflow" package (Version 1.4.0). Sequencing quality was assessed using sequencing saturation, and all 72 regions-of-interest (ROIs) exceeded the recommended 50% saturation threshold. Gene expression was considered detectable when it exceeded the limit of quantification (LOQ2), defined as two geometric standard deviations above the geometric mean of negative control probes. Genes detected in at least 2% of segments were retained for downstream analysis. Using this criterion, 11,537 of 18,677 genes were detected above LOQ2. Prior to subsequent analyses, expression values were normalized using Q3 normalization.

GeoMx DSP quantifies RNA expression using a hybridization-based, tiled probe design targeting short transcript regions, as described previously (19). This design enables robust gene detection from highly fragmented FFPE RNA and does not depend on intact RNA integrity metrics such as RNA integrity number or DV200. Consistent with this design principle, prior validation studies have demonstrated that gene detection performance is well preserved even at low DV200 levels (approximately 5–10%) (20). Accordingly, RNA quality assessment in our GeoMx DSP analysis was performed using

platform-specific quality control metrics rather than RNA integrity–based measures.

Validation of cell type specificity in selected ROIs via marker gene expression

To confirm the cell type enrichment within the selected ROIs, we compiled a comprehensive list of marker genes specific to hepatocytes, hepatic stellate cells (HSCs), and immune cells. The marker gene list was obtained from various sources, including PanglaoDB (21), CellMarker 2.0 (22), and a manual literature search focusing on HSC activation markers (Table S2) (8, 23-27). We then utilized the spatial transcriptomics data to evaluate the expression levels of these marker genes within each ROI. To determine the statistical significance of the differences in marker gene expression across the ROIs, we performed a one-way analysis of variance (ANOVA) test. A heatmap was generated to visualize the relative expression patterns of the marker genes across the different ROIs, providing a clear overview of the cell type specificity within each region.

Gene set enrichment analysis (GSEA) & gene set variation analysis (GSVA) in our GeoMx DSP dataset

To construct the pathway gene sets for analysis, we compiled a comprehensive set of genes from two distinct sources: the human Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway gene set (1), and curated pathway gene sets derived from literature known to be associated with MASH (2-17). The human KEGG pathway gene sets served as foundational components. Additionally, we curated pathway gene sets from relevant literature focused on MASH. This involved an extensive review of publications detailing molecular pathways implicated in the pathogenesis of MASH. Genes identified in these studies were included in our curated pathway gene sets. GSEA was employed to interpret the biological relevance of our transcriptomic data (28, 29). We utilized two gene set collections: Human KEGG pathway gene sets and our curated MASH-associated pathway gene sets. It is noted that, in GSEA, some gene sets were excluded in specific ROIs due to irrelevance of the gene sets on the ROIs (Table S3). For GSEA, genes were

ranked based on the t -statistics derived from the covariate-adjusted limma models (age, sex, and body mass index [BMI]), with statistical significance assessed using 1,000 gene set permutations. Enriched pathways were identified based on normalized enrichment scores, offering insights into the molecular pathways associated with MASH. We utilized the R package GSVA to generate individual scores for pathway gene sets (30).

Analyses of publicly available datasets of single-cell/single-nuclei RNA-Seq (sc/snRNA-Seq) for the human liver with MASH

Most of the public human liver sc/snRNA-Seq datasets we analyzed were generated before the terminology changed from NASH to MASH; however, here, we used the term MASH throughout the manuscript according to recent guidelines (31). In order to assess the expression levels of cytochrome P450 (CYP450) genes in immune cells and HSCs in the liver tissue of patients with MASH, we obtained and reanalyzed publicly available scRNA-Seq and snRNA-Seq datasets (Gene Expression Omnibus [GEO] accessions: GSE159977 and GSE212837) (32, 33). The scRNA-Seq analysis was conducted utilizing the R package Seurat v.4.3.0 (34). During the preprocessing of the scRNA-Seq data, we filtered out cells that had fewer than 200 uniquely expressed genes, following the default parameter settings of the package. Only genes expressed in at least ten cells were considered for subsequent analysis. Additionally, we conducted quality control for scRNA-Seq data using default parameters for miQC package v.1.6.0. to remove low quality cells which may be caused by their damaged membranes (35). After applying the quality control, we obtained cells with less than 8% mitochondrial gene fraction. For an snRNA-Seq data analysis, we acquired a pre-processed dataset that already included assigned cell types. Only genes expressed in at least ten cells were considered for subsequent analysis. We then analyzed the data for HSCs using the default settings of the Seurat package (34).

Generation and analysis of human liver bulk RNA-Seq data from our GMC cohort

(MASH versus NonMASH)

The bulk RNA-Seq analysis of our GMC MASLD cohort was conducted as follows. We prepared paired-end RNA libraries preparation for 18 liver samples from subjects with varying degrees of MASH. These libraries were subsequently sequenced at Macrogen, Inc. (Seoul, Korea) using the TruSeq Stranded mRNA LT Sample Prep Kit (Illumina, San Diego, CA, USA) following the manufacturer's instructions. The initial raw read data underwent trimming using Trimmomatic v0.38 (36), and quality control analysis was performed using FastQC v0.11.7. The resulting trimmed reads were aligned to the human reference genome (GRCh38) using HISAT2 v2.1.0 (37). Subsequently, the aligned reads were assembled using StringTie v2.1.3b (38). For DEG analysis, we employed raw read counts in conjunction with edgeR v3.18 (39). DEG analyses comparing MASH and NonMASH were conducted using the criteria: $p < 0.05$ and $|\log_2 \text{fold change}| > 0.25$.

Ligand–receptor interactions between ROIs in our GeoMx DSP dataset

Ligand–receptor interactions between ROIs were calculated separately to suppose interactions that are differential microenvironment in each ROI. Known ligand–receptor pairs were obtained from CellPhoneDB v2.0 (40).

For each ligand–receptor pair, we performed a statistical analysis method using the `cpdb_statistical_analysis_method` function within the CellPhoneDB python package. To ensure robust statistical inference, we utilized 1,000 permutations to generate a null distribution of mean expression levels, and a threshold of 0.1 was applied to include only genes expressed in at least 10% of the ROIs within a group. Interaction scores were calculated by enabling the `score_interactions` parameter, and only ligand–receptor pairs with a $P < 0.05$ were considered statistically significant for further analysis.

Ligand–receptor interactions between ROIs were calculated separately to identify specific interactions in different microenvironments and MASH progression. We then utilized one-way ANOVA to analyze the differences in expression levels of each significant ligand–receptor pair across MASH subgroups. To identify specific pairwise differences between subgroups, a post-hoc Tukey's honestly significant difference

analysis was performed using R software, with an adjusted p -value < 0.05 considered significant.

For the additional ligand–receptor pair analysis in compartment-blind manner, all 72 ROIs were first pooled under a single tissue-wide label using CellPhoneDB v5.0, removing ROI-segment distinction. Interactions were retained if both partners were detected in at least 90% of ROIs and in all 24 patients, and reached statistical significance (permutation $p < 0.05$, 1,000 permutations) in at least one of the nine segment-resolved sender→receiver pairs from a parallel, segment-labeled CellPhoneDB run. Expression values from the three ROIs within each patient were then averaged to generate a single expression profile per patient ($n = 24$; 8 per MASH stage). This patient-level averaging served to (1) eliminate pseudoreplication arising from multiple ROIs per patient and (2) retain only interactions detectable across transcriptionally distinct compartments. Then, association between interaction level and MASH stage was assessed for each interaction using the Wilcoxon rank-sum test in a one-vs-rest manner. For each interaction, pairwise differences between individual stages were additionally compared using Student's t -test.

Immunofluorescence (IF) staining for protein-level validation

IF staining was performed on FFPE human liver sections from a subset of subjects with sufficient remaining tissue, comprising NonMASH ($n = 8$) and MASH ($n = 10$), using the GeoMx DSP platform (NanoString Technologies, Seattle, WA, USA). Owing to tissue exhaustion, the number of evaluable cases for albumin-enriched ROIs was slightly reduced, with one fewer MASH sample included in the analysis.

The following primary antibodies were used: anti–Cytochrome P450 1A2 antibody (clone EPR6138(2), Abcam, Cambridge, UK; 1:100), anti–IL32 rabbit polyclonal antibody (Abcam; 1:100), anti–S100A8 + S100A9 antibody (clone RM1038, Abcam; 1:500), anti-CD45 (Novus Biologicals, Centennial, CO, USA; 1:40), anti-vinculin (clone 7F9, Alexa Fluor® 647–conjugated, Santa Cruz Biotechnology, Dallas, TX, USA; 1:50), and anti-albumin (clone F-10, Alexa Fluor® 488–conjugated, Santa Cruz Biotechnology; 1:50). Nuclear counterstaining was performed using Syto13 (Thermo Fisher Scientific,

Waltham, MA, USA; 1:10) or TO-PRO™-3 iodide (642/661; Thermo Fisher Scientific; 1:1000).

Statistics and visualization

Paired-sample t-tests were used to compare the expression of each gene before and after BS in the GSE106737 dataset (41). Associations between gene expression and clinical or histologic parameters were assessed using partial correlation analyses implemented via multivariable linear regression models adjusting for age, sex, and BMI. All reported P-values are two-sided, and $P < 0.05$ was considered statistically significant for other analyses. For visualization, the pheatmap (v1.0.12), ggplot2 (v3.3.0), and circlize (v0.4.15) packages were utilized (42-44).

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