Supplemental Materials

Dysregulation of murine long non-coding single cell transcriptome

in non-alcoholic steatohepatitis and liver fibrosis

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Supplemental Tables S1-S8 (Excel workbooks)

GTF file: gtf76k_mm10_Liver_scRNAseq.gtf

Loupe Browser files:

1_Control_Liver_scRNAseq.cloupe (300 MB)
2_Chow_NASH_NAFLD.cloupe (525 MB)
3_Healthy_CCl4_Mesenchyme.cloupe (250 MB)

Supplementary Figure legends

Fig. S1 – Identification of liver cell clusters from healthy mouse liver. A. Dot plot showing average expression values for marker genes (shown along X-axis) across the 13 hepatic cell clusters (Y-axis) shown in the UMAP in Fig. 2A. Those cell clusters were based on hepatocytes and NPCs from four datasets from control mouse livers. **B.** Dot plot showing average expression values for marker genes (shown along X-axis) across the 12 hepatic cell clusters (Y-axis) shown in the UMAP in Fig. 4A. Those cell clusters were based on liver cells isolated from healthy mice (chow-fed diet), and from mice fed HFHFD for 15 wk to induce simple steatosis (NAFLD), or for 30-34 wk to induce NASH.

Fig. S2 – Kupffer cell subpopulations. Feature plots presenting marker gene expression for Trem2, and for 4 lncRNAs that are markers for different Kupffer subpopulations. UMAP is as shown in Fig. 4G.

Fig. S3 – Shared network-essential regulators in healthy and diseased (NAFLD and NASH) mouse livers. Venn diagram showing overlap between network-essential PCGs and lncRNAs from control, NAFLD and NASH gene regulatory networks from Fig. 6 and Table S5.

Fig. S4 – Ctcflos regulation of Pck1. Subnetwork showing Ctcflos (lnc2065), an essential network regulatory gene in the NASH network, which makes connections with Pck1 via lnc10621.

Fig. S5 – Differentiation of quiescent HSCs into myofibroblasts. A. UMAP showing HSCs zonation clusters (top *left*) and corresponding DotPlot of known HSC marker genes (top *right*). Shown are feature plots for genes that are markers for quiescent HSCs (Ecm1, Rgs5) and for activated HSCs (myofibroblast) (Col1a1, Col1a2). **B.** Heatmap showing relative expression patterns for PCGs that are differentially expressed between quiescent pericentral HSCs and myofibroblasts from CCl_4-exposed mouse liver mesenchymal cells, along with their top functional enrichment terms, listed on the right. See Fig. 7E for corresponding heat map for lncRNA genes.

Fig. S6 – Feature plots showing examples of lncRNAs that are differentially expressed across multiple mesenchymal cell subpopulations.

Fig. S7 – Shared gene regulatory network regulators in healthy and CCl_4-induced fibrotic liver. Venn diagram showing overlap between network-essential PCGs and lncRNAs from the healthy and fibrotic liver gene regulatory networks shown in Fig. 8.See details in Table S5.

Fig. S8 – Clustering of 39 regulatory lncRNAs from chow-fed (control) liver gene regulatory network. **Top**: PCG targets that make a direct connection with regulatory lncRNAs in the chow fed liver network of Fig. 6A were provided as input to Metascape to obtain top functional enrichment terms based on -log10 (P-value). The color scale represents -log10(P) values, with darker purple coloration indicating more significant p-values. Two-way hierarchical clustering of the functional enrichment heatmap split the 39 lncRNAs into 3 clusters (columns colors) based on their patterns of shared functions. Target genes of lncRNAs from two of the major functional clusters (green, blue) were variously enriched for diverse metabolic processes, and a third (yellow) was functionally enriched for angiogenesis and vasculature development, extracellular matrix, and cell-cell adhesion, as shown on the right. **Bottom**: subnetwork of the network shown in Fig. 6A. This subnetwork is comprised of the network-essential 39 regulatory lncRNAs and their target genes, which clustered to give gene modules that mirror the clustering results obtained for the same lncRNAs based on their functional group enrichments, shown on top. The subnetwork was derived from the network in Fig. 6A by removing all PCG regulators and their gene targets, and by retaining regulatory lncRNAs and their direct protein coding genes connections, which were used as input for the functional enrichment analysis shown at the top. The regulatory lncRNAs (nodes) are color coded to match the lncRNA cluster colors shown in the heat map. Gene targets for lnc6251 (bottom, gray node) did not show enrichment for any functional terms and was therefore excluded from the enrichment heatmap (top).

Fig. S9 – Clustering of 28 regulatory lncRNAs from NAFLD gene regulatory network. **Top**: Analysis of network-essential regulatory lncRNAs from NAFLD network of Fig. 6B, as described in Fig. S8. Two-way hierarchical clustering identified 3 clusters of regulatory lncRNAs, with target genes of lncRNAs from cluster blue enriched for carboxylic acid and other metabolic processes, cluster green lncRNA targets enriched for vasculature development, angiogenesis, hippo signaling, extracellular matrix and cell motility, and the target genes of lncRNAs from cluster yellow, which is comprised of only 2 lncRNAs (lnc6840, lnc12750), specifically enriched for import across plasma membrane and ion transport. **Bottom**: subnetwork of the network shown in Fig. 6B. It is comprised of the 28 regulatory lncRNAs and their target genes (excluding regulatory PCGs) and was obtained as described in Fig. S8. The 28 regulatory lncRNAs clustered to give gene modules that mirror the clustering results obtained for the same lncRNAs based on their functional group enrichments, shown on top.

Fig. S10 – Clustering of 25 regulatory lncRNAs from NASH gene regulatory network. **Top**: Analysis of network-essential regulatory lncRNAs from NASH network of Fig. 6C, as described in Fig. S8. Two-way hierarchical clustering identified 4 clusters of regulatory lncRNAs, with the target genes of lncRNAs from cluster green enriched for vasculature development, angiogenesis, and cell motility, and with a subset of lncRNAs in this cluster enriched for extracellular matrix, wound healing, and regulation of Wnt signaling. The target genes of lncRNAs from cluster yellow (n=3 lncRNAs) were enriched for inflammatory response gene targets, while the target genes of lncRNAs from cluster orange (n=2 lncRNAs) were enriched for cation transmembrane transport. The targets of cluster blue lncRNAs (n=5) were enriched for carboxylic acid and other metabolic processes. **Bottom**: subnetwork of the network shown in Fig. 6C. It is comprised of the 25 regulatory lncRNAs and their target genes (excluding regulatory PCGs) and was obtained as described in Fig. S8. The 25 regulatory lncRNAs clustered to give gene modules that mirror the clustering results obtained for the same lncRNAs based on their functional group enrichments, shown on top.

Fig. S11 – Combined clustering of 92 regulatory lncRNAs from Chow, NAFLD and NASH liver gene regulatory networks. Shown is a merged functional enrichment heatmap showing the top enriched terms (as rows) for genes targets of all network-essential regulatory lncRNAs (as columns) from the chow, NAFLD, and NASH networks combined and analyzed as described in Fig. S8. The NAFLD and NASH network-derived regulatory lncRNAs showed more extensive and more significant enrichment for vasculature development and angiogenic processes than those from control liver, whereas the NAFLD and control network regulatory lncRNAs both

showed enrichment for diverse metabolic processes. Many fewer regulatory lncRNAs showed target gene enrichment for immune-related processes. Overall, this figure compares regulatory lncRNAs and their target functional terms across biological conditions.

Fig. S12 – Clustering of 19 regulatory lncRNAs from healthy liver mesenchymal cell gene regulatory network. **Top**: Analysis of network-essential regulatory lncRNAs from the healthy liver mesenchymal network of Fig. 8A, as described in Fig. S8. Two-way hierarchical clustering identified 2 clusters of regulatory lncRNAs, with the target genes of lncRNAs from cluster blue (n=5 lncRNAs) significantly enriched for terms related to muscle contraction, notch signaling, and ion homeostasis, and those of cluster yellow (n=14 lncRNAs) strongly enriched for diverse biological processes, including cell morphogenesis, regulation of defense response, vascular development, and interferon responses. **Bottom**: subnetwork of the network shown in Fig. 8A. It is comprised of the 19 regulatory lncRNAs and their target genes (excluding regulatory PCGs) and was obtained as described in Fig. S8. The 19 regulatory lncRNAs clustered to give gene modules that mirror the clustering results obtained for the same lncRNAs based on their functional group enrichments, shown on top.

Fig. S13 – Clustering of 26 regulatory lncRNAs from CCl_4-induced liver fibrosis gene regulatory network. **Top**: Analysis of network-essential regulatory lncRNAs from the CCl_4-treated mesenchymal cell network of Fig. 8B, as described in Fig. S8. Two-way hierarchical clustering identified 3 clusters of regulatory lncRNAs (blue, green, yellow), with the target genes of lncRNAs from these clusters respectively showing strongest enrichments and greatest specificities for: muscle contraction and notch signaling and related processes (blue); extracellular matrix organization and other terms (green); and cell junction assembly, response to interferon-beta, and other terms (yellow). **Bottom**: subnetwork of the network shown in Fig. 8B. It is comprised of the 26 regulatory lncRNAs and their target genes (excluding regulatory PCGs) and was obtained as described in Fig. S8. The 26 regulatory lncRNAs clustered to give gene modules that mirror the clustering results obtained for the same lncRNAs based on their functional group enrichments, shown on top.

Fig. S14 – Combined clustering of 45 network-essential regulatory lncRNAs from Healthy and CCl_4-induced liver fibrosis gene regulatory networks. Shown is a merged functional enrichment heatmap showing the top enriched terms (as rows) for genes targets of all network-essential regulatory lncRNAs (as columns) from the healthy and fibrotic liver mesenchymal gene regulatory networks combined and analyzed as described in Fig. S8. Shown are pathways that were either common or specific to control versus CCl_4-treated mesenchymal lncRNA gene targets. Overall, this figure compares regulatory lncRNAs and their target functional terms across two biological conditions.

Fig. S15 – LncRNA-PCG regulatory network based on genes predicted to be involved in lncRNA-genomic DNA triplex binding. Shown are regulatory subnetworks for those lncRNAs that are enriched for forming triplex interactions (based on TDF analysis) with their protein coding gene (PCG) targets identified using bigSCale2 gene regulatory networks from Chow diet (control) liver (**A**), NAFLD liver (**B**), and NASH liver (**C**) (see Fig. 6). The networks shown here are subsets of those shown at the bottom of Fig. S12 and Fig. S13, respectively, insofar as only the regulatory lncRNAs and their protein-coding gene targets that form triplexes based on TDF are shown.

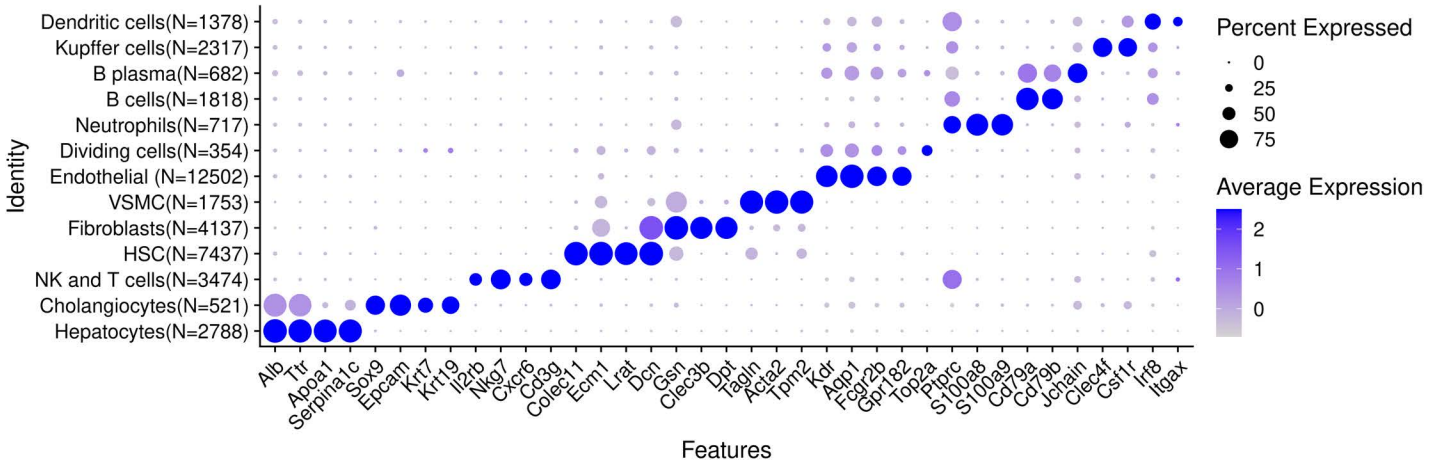
Fig. S16 – LncRNA-PCG regulatory network based on genes predicted to be involved in lncRNA-genomic DNA triplex binding. Shown are regulatory subnetworks for those lncRNAs that are enriched for forming triplex interactions (based on TDF analysis) with their PCG targets identified using bigSCale2 gene regulatory networks for mesenchymal cells from control liver (**A**) and from CCl_4-induced fibrotic liver (**B**) (see Fig. 8). The networks shown here are subsets of those shown at the bottom of Figs. S8, S9 and S10, respectively, insofar as only the regulatory lncRNAs and their protein-coding gene targets that form triplexes based on TDF are shown. **Example**: In Fig. 8A, the lncRNA Meg3 is connected to many PCGs and lncRNAs, some of which have their own connections. In Fig. S12, where only regulatory lncRNAs and their direct connections with other regulatory lncRNAs or protein coding genes are shown, Meg3 is in an isolated subnetwork comprised only of its direct target genes. Finally, in Fig. S16A, the subnetwork with Meg3 is also in an isolated subnetwork, one that has

even fewer genes than in Fig. S12, because only the targets that are predicted to form a triplex with Meg3 are shown.

Fig. S17 – Macrophage proliferation. Violin plots showing expression of genes related to cell division (Top2a and Stmn1) in proliferating Kupffer cells (from Fig. 4G).

Fig. S1

A.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Kupffer cells(N=2317)
B plasma(N=682)
B cells(N=1818)
Neutrophils(N=717)
Dividing cells(N=354)
Endothelial (N=12502)
VSMC(N=1753)
Fibroblasts(N=4137)
HSC(N=7437)
NK and T cells(N=3474)
Cholangiocytes(N=521)
Hepatocytes(N=2788)
Identity
Alb Ttr Apoa1 Serpina1c Sox9 Epcam Krt7 Krt19 Il2rb Nkg7 Cxcr6 Cd3g Colec11 Ecm1 Lrat Dcn Gsn Clec3b Dpt Tagln Acta2 Tpm2 Kdr Aqp1 Fcgr2b Gpr182 Top2a Ptprc S100a8 S100a9 Cd79a Cd79b Jchain Clec4f Csf1r Irf8 Itgax
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Percent Expressed
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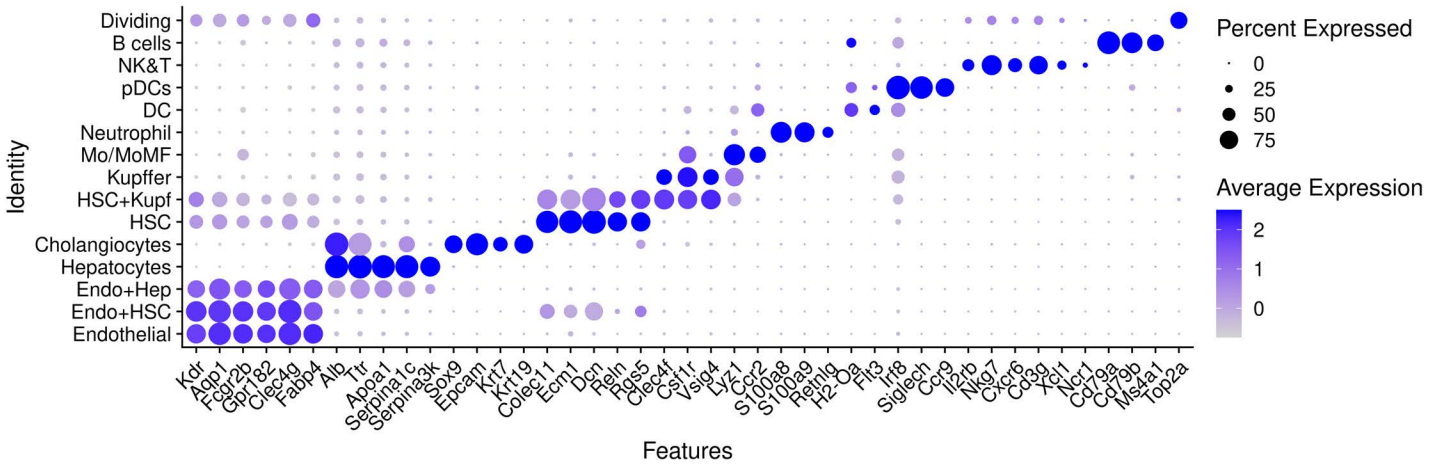
25
50
75
Average Expression
2
1
0

B.


Dividing
B cells
NK&T
pDCs
DC
Neutrophil
Mo/MoMF
Kupffer
HSC+Kupf
HSC
Cholangiocytes
Hepatocytes
Endo+Hep
Endo+HSC
Endothelial
Identity
Kdr Aqp1 Fcgr2b Gpr182 Clec4g Fabp4 Alb Ttr Apoa1 Serpina1c Serpina3k Sox9 Epcam Krt7 Krt19 Colec11 Ecm1 Dcn Rein Rgs5 Clec4f Csf1r Vsig4 Lyz1 Ccr2 S100a8 S100a9 Retnlg H2-Oa Flt3 Irf8 Siglech Ccr9 Il2rb Nkg7 Cxcr6 Cd3g Xcl1 Ncr1 Cd79a Cd79b Msa4a1 Top2a
Features
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50
75
Average Expression
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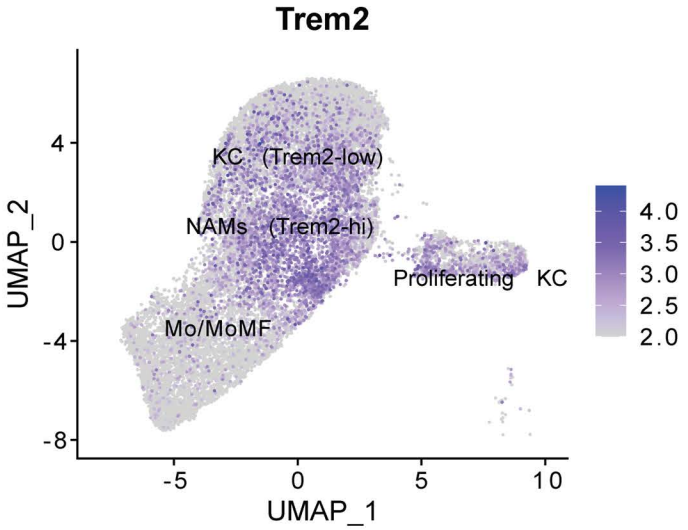
1
0

Fig. S2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KC (Trem2-low)
NAMs (Trem2-hi)
Proliferating KC
Mo/MoMF
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UMAP_1
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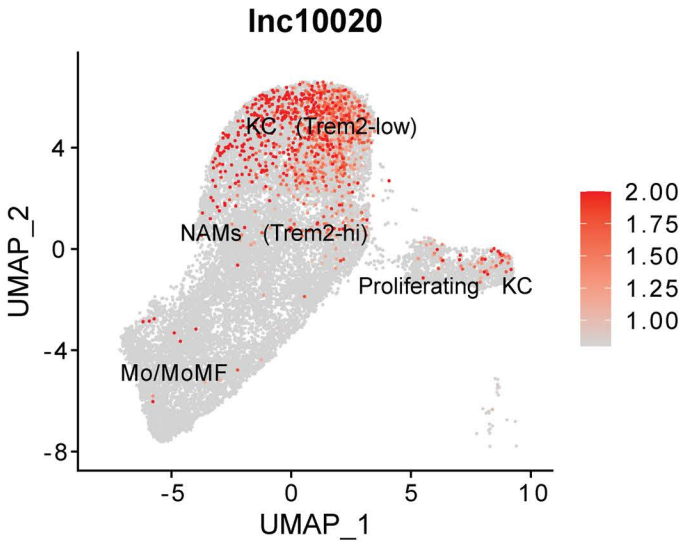
3.0
2.5
2.0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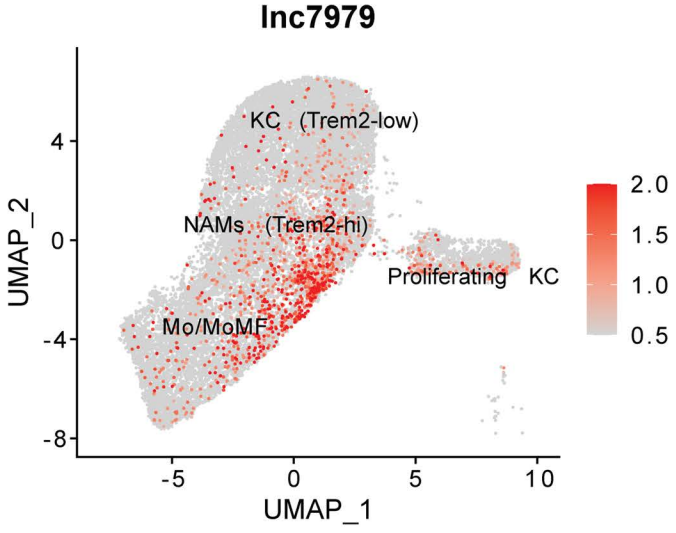
1.00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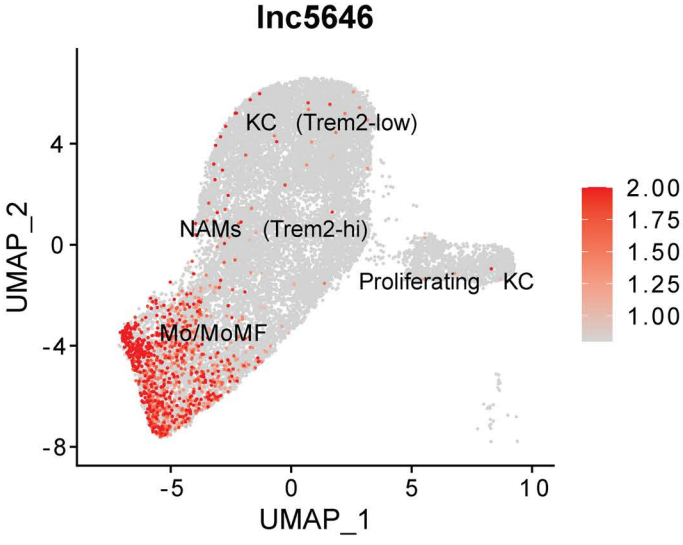
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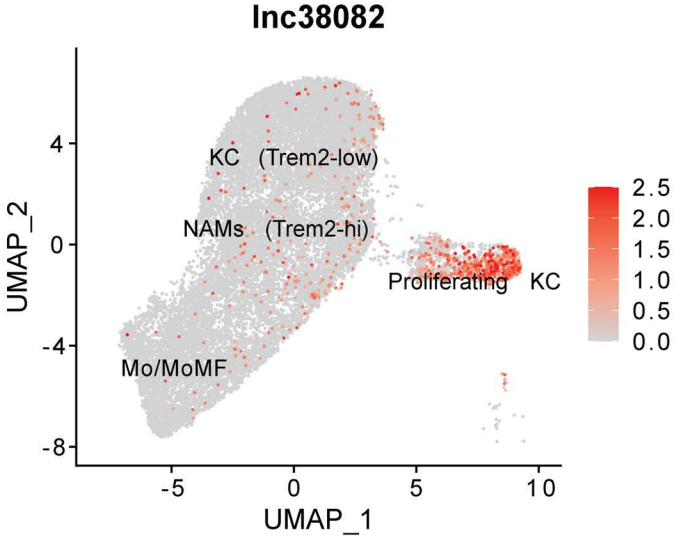
1.00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NAMs (Trem2-hi)
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UMAP_1
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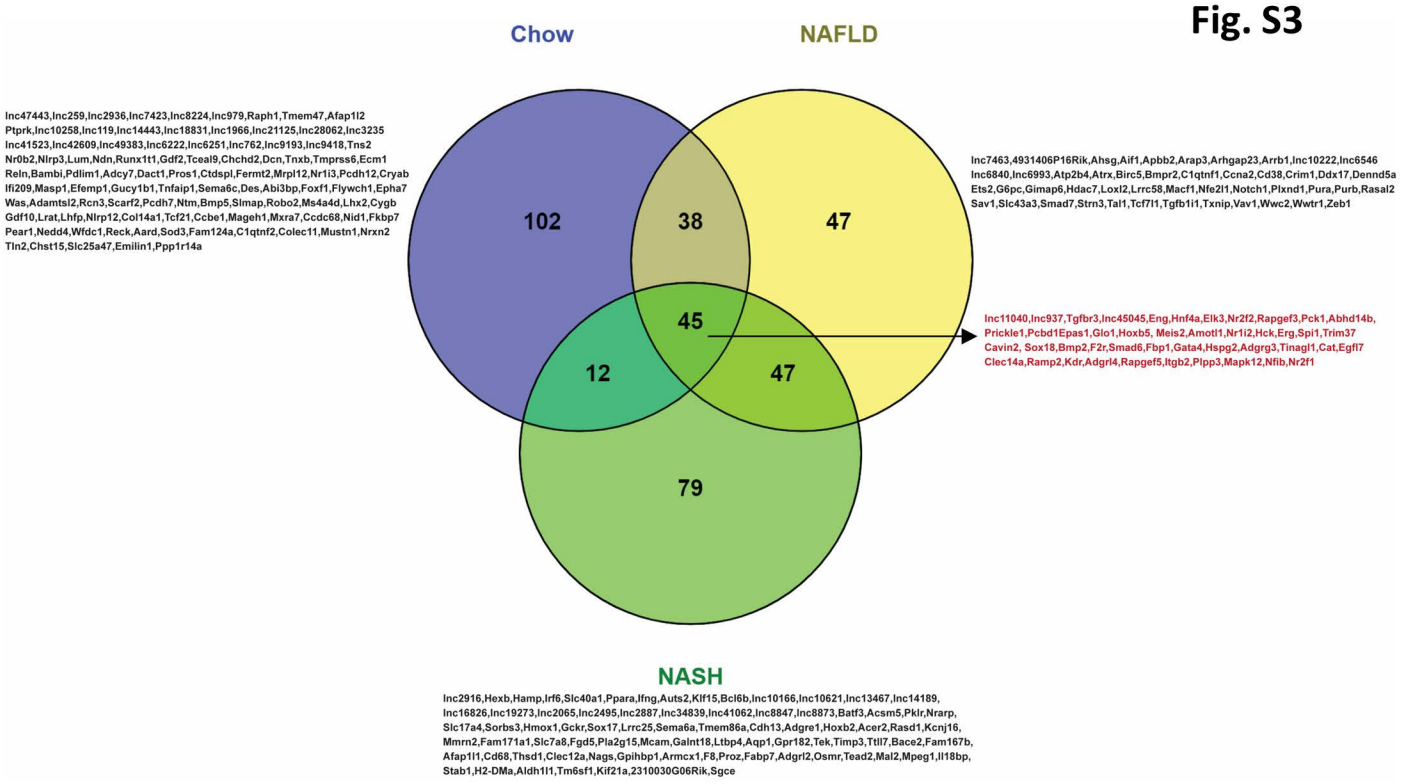
0.0

Fig. S3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38
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Mmrn2,Fam171a1,Slc7a8,Fgd5,Pla2g15,Mcam,Galnt18,Ltbp4,Aqp1,Gpr182,Tek,Timp3,Ttll7,Bace2,Fam167b,
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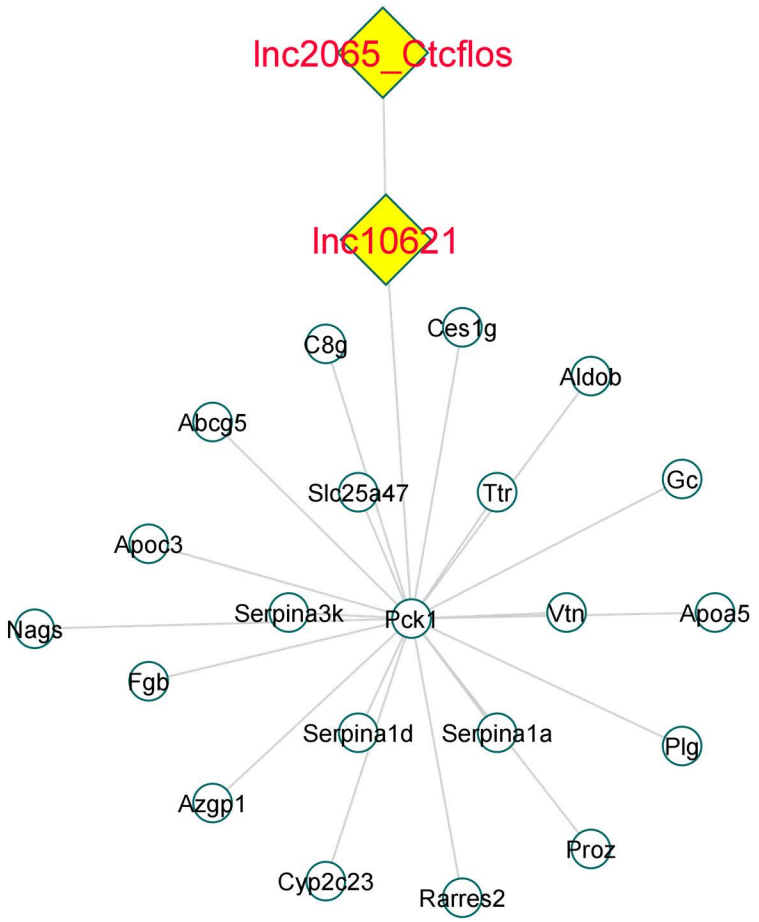
Fig. S4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Pck1
Vtn
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Plg
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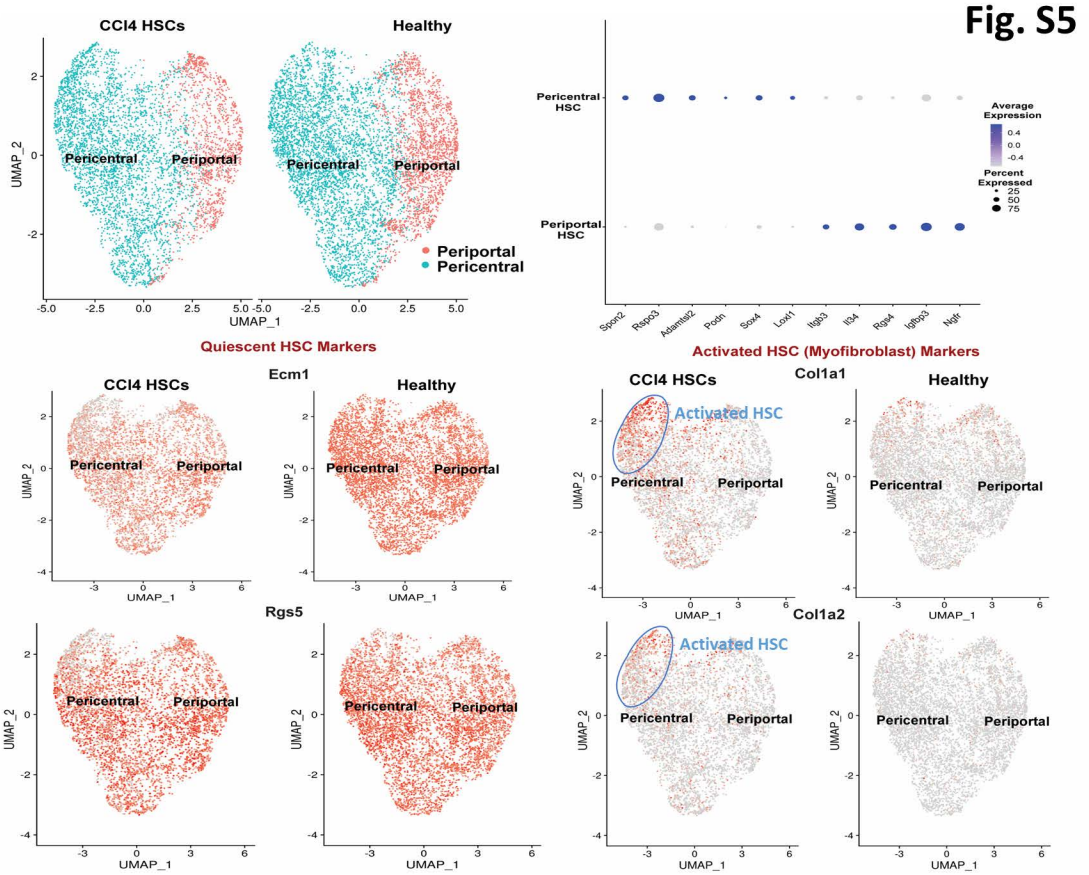
Proz
Cyp2c23
Rarres2

A.

Fig. S5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Healthy
Pericentral
Periportal
UMAP_1
UMAP_2
Periportal
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Pericentral HSC
Periportal HSC
Average Expression
Percent Expressed
Spon2
Rspo3
Adamts2
Podn
Sox4
Loxl1
Itgb3
Il34
Rgs4
Igfbp3
Ngfr
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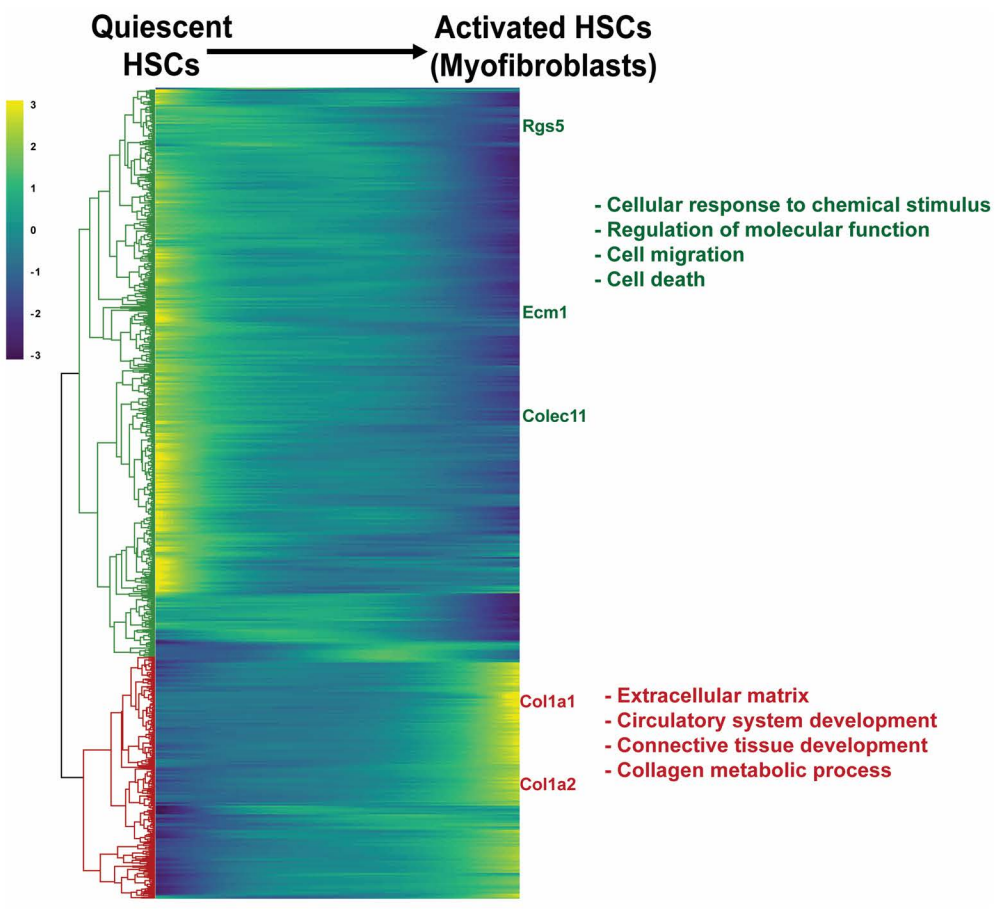
Activated HSC (Myofibroblast) Markers
Ecm1
Col1a1
Rgs5
Col1a2
Activated HSC

B.


Quiescent HSCs
Activated HSCs (Myofibroblasts)
Rgs5
Ecm1
Colec11
Col1a1
Col1a2
- Cellular response to chemical stimulus
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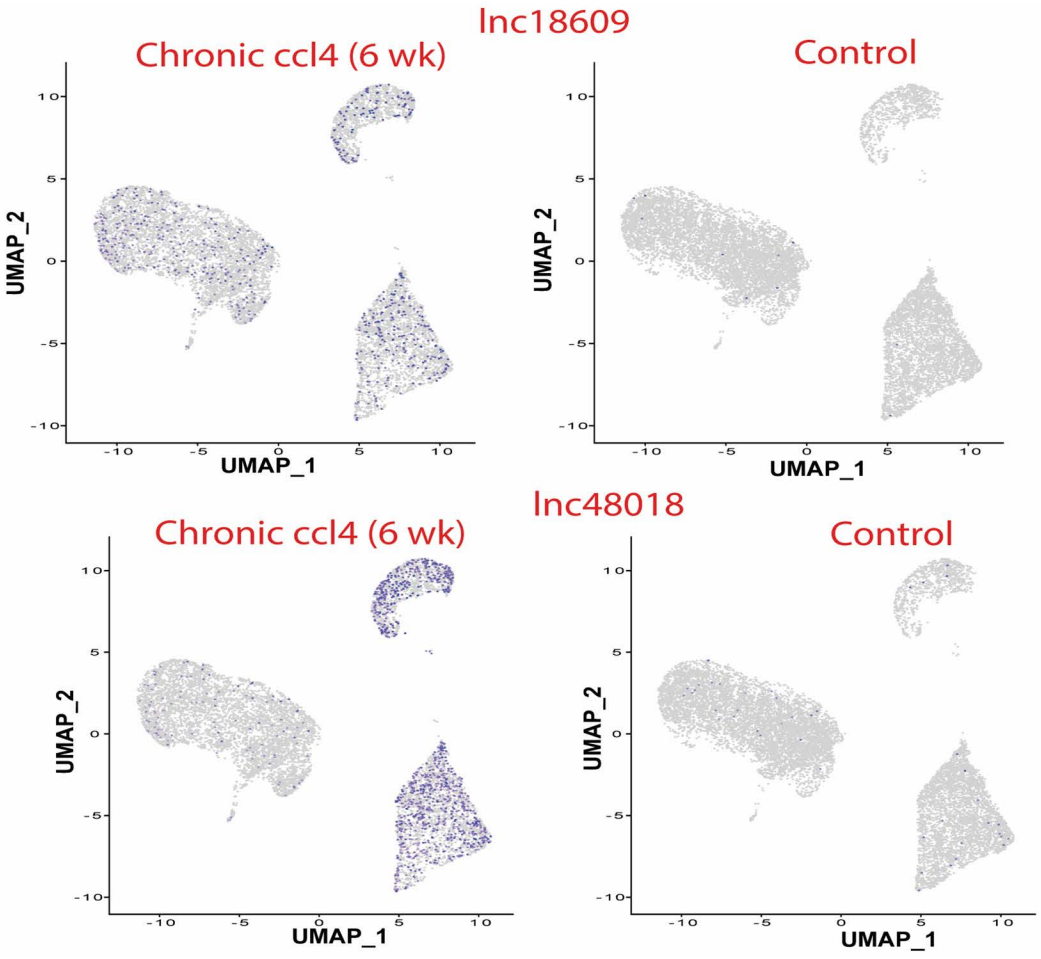
- Cell migration
- Cell death
- Extracellular matrix
- Circulatory system development
- Connective tissue development
- Collagen metabolic process

Fig. S6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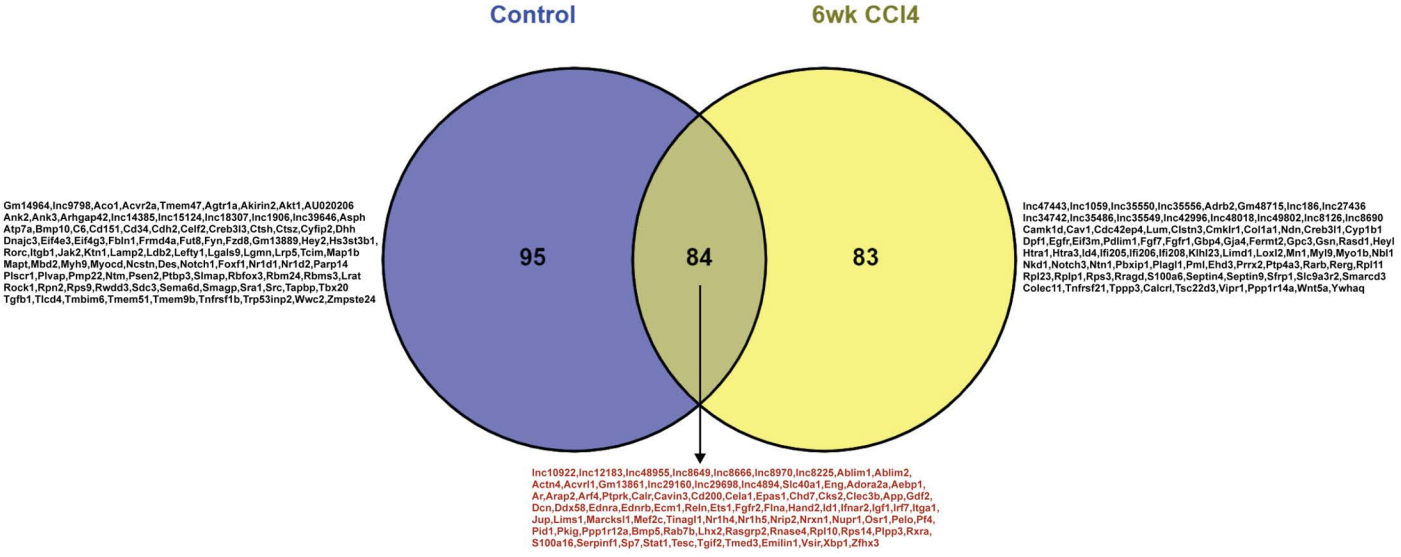
Control
lnc48018
Chronic ccl4 (6 wk)
Control
UMAP_1
UMAP_2

Fig. S7


Control
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84
83
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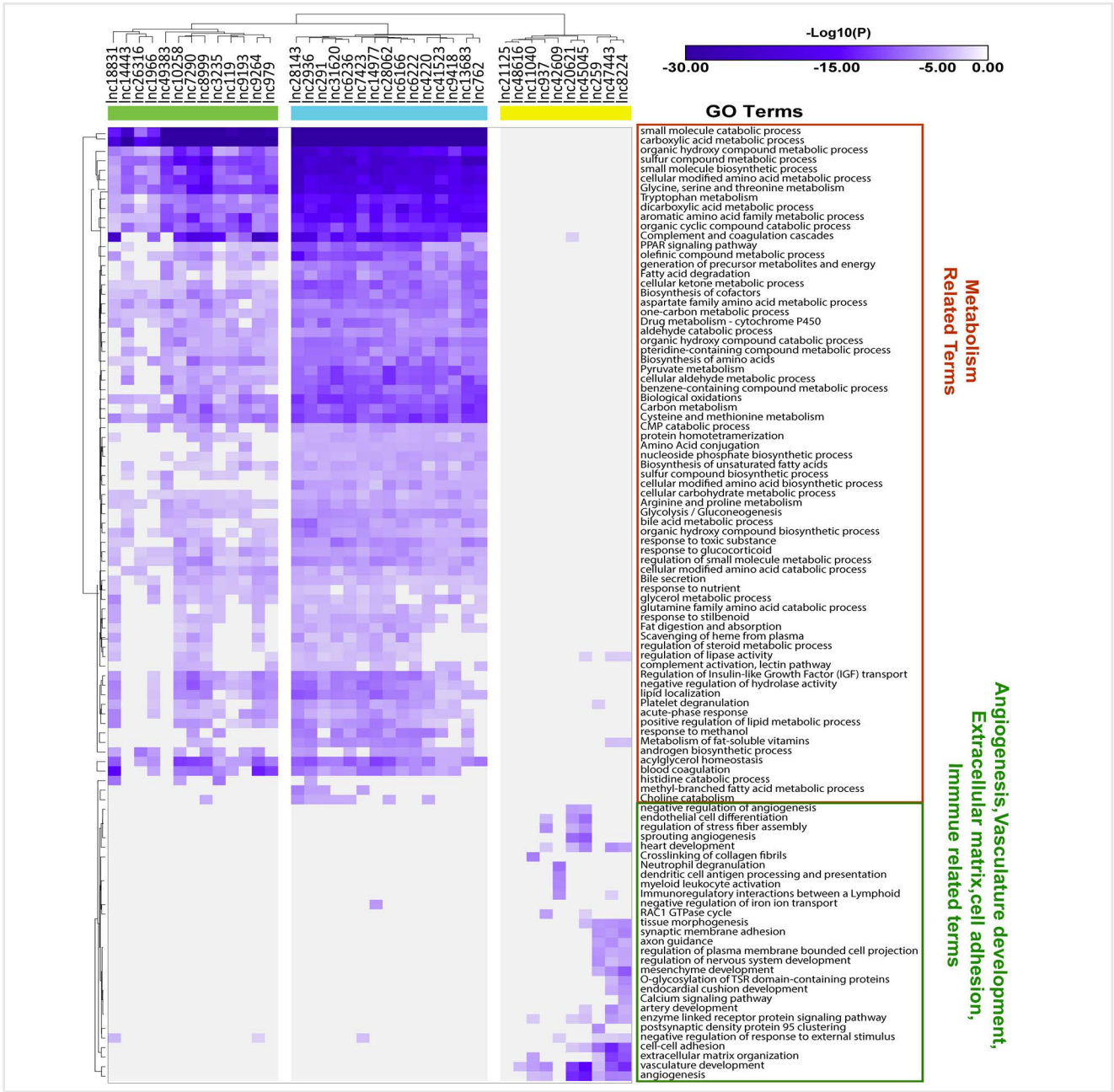
Dcn,Ddx58,Ednra,Ednrb,Ecm1,Reln,Ets1,Fgfr2,Flna,Hand2,Id1,Ifnar2,Igf1,Irf7,Itga1,
Jup,Lims1,Marcksl1,Mef2c,Tinagl1,Nr1h4,Nr1h5,Nrip2,Nrxn1,Nupr1,Osr1,Pelo,Pf4,
Pid1,Pkig,Ppp1r12a,Bmp5,Rab7b,Lhx2,Rasgrp2,Rnase4,Rpl10,Rps14,Ptpp3,Rxra,
S100a16,Serpinf1,Sp7,Stat1,Tesc,Tgif2,Tmed3,Emilin1,Vsir,Xbp1,Zfhx3

Fig. S8 (Chow diet)



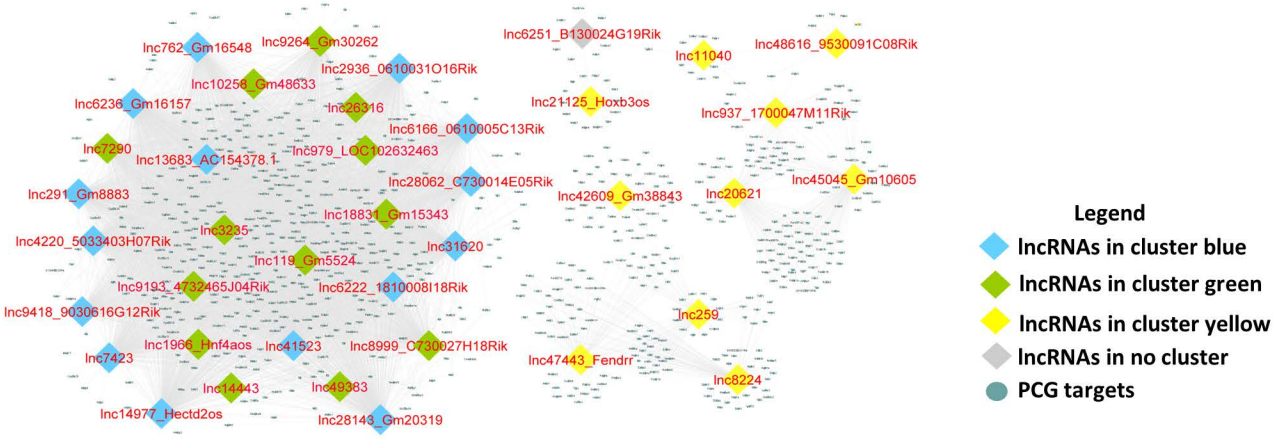
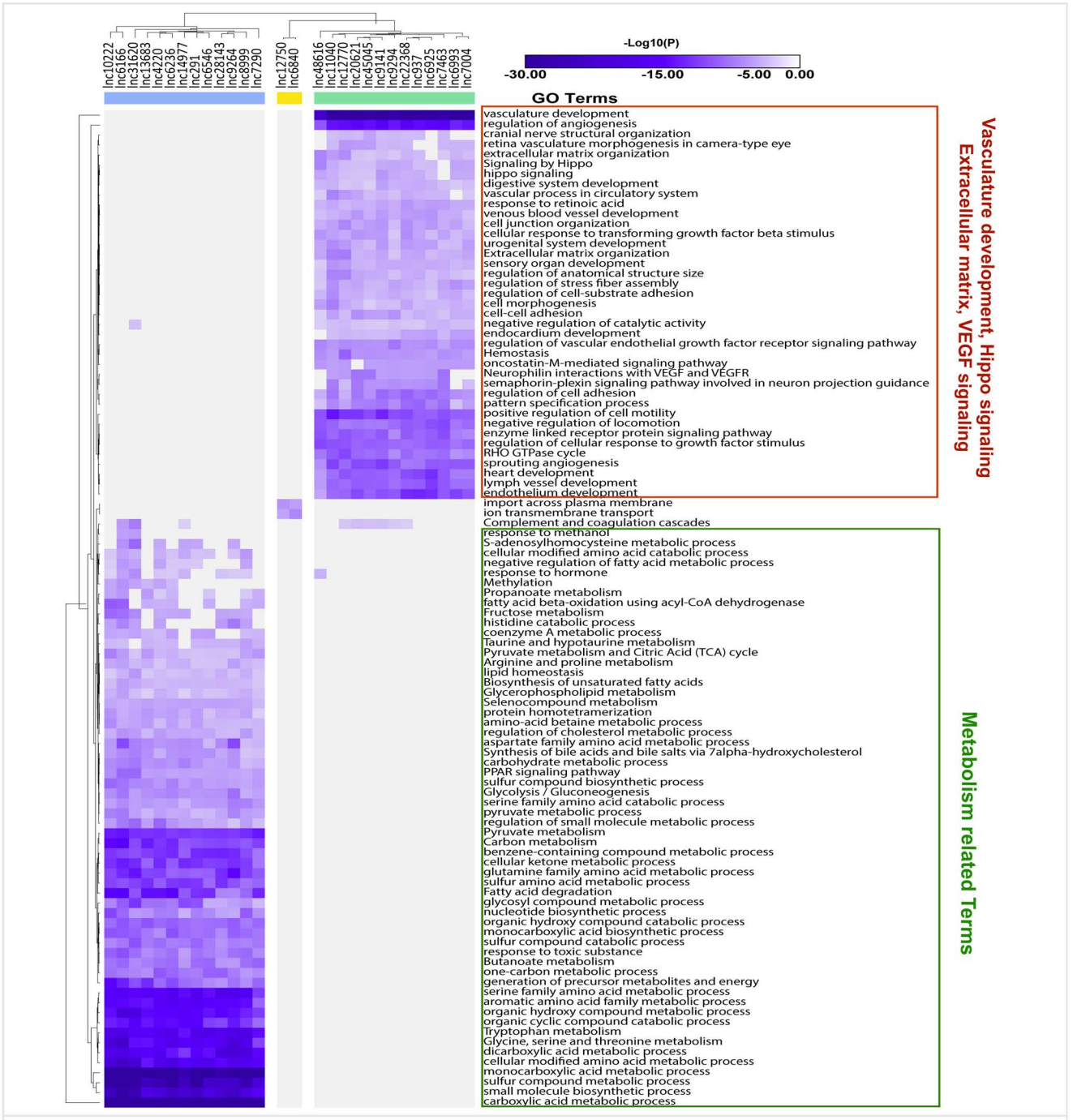


Fig. S9 (NAFLD)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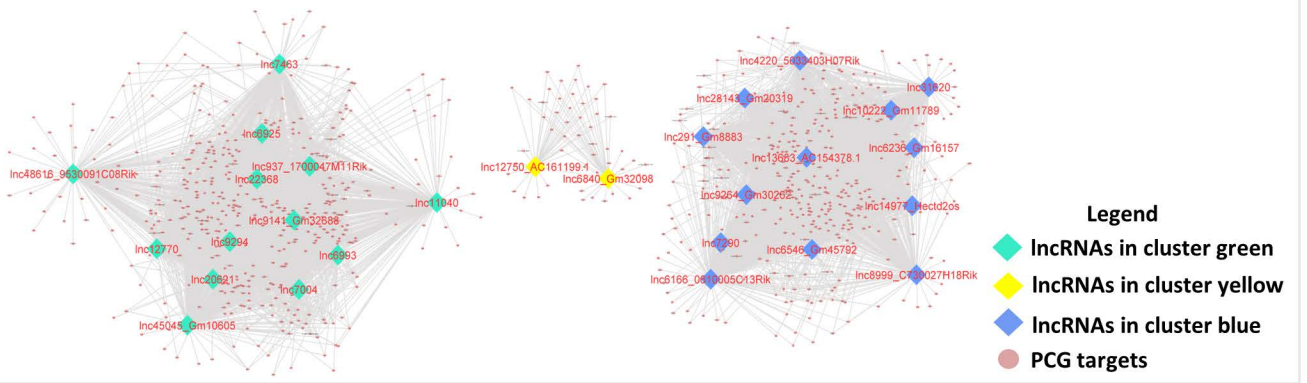
GO Terms
vasculature development
regulation of angiogenesis
cranial nerve structural organization
retina vasculature morphogenesis in camera-type eye
extracellular matrix organization
Signaling by Hippo
hippo signaling
digestive system development
vascular process in circulatory system
response to retinoic acid
venous blood vessel development
cell junction organization
cellular response to transforming growth factor beta stimulus
urogenital system development
Extracellular matrix organization
sensory organ development
regulation of anatomical structure size
regulation of stress fiber assembly
regulation of cell-substrate adhesion
cell morphogenesis
cell-cell adhesion
negative regulation of catalytic activity
endocardium development
regulation of vascular endothelial growth factor receptor signaling pathway
Hemostasis
oncostatin-M-mediated signaling pathway
Neurophilin interactions with VEGF and VEGFR
semaphorin-plexin signaling pathway involved in neuron projection guidance
regulation of cell adhesion
pattern specification process
positive regulation of cell motility
negative regulation of locomotion
enzyme linked receptor protein signaling pathway
regulation of cellular response to growth factor stimulus
RHO GTPase cycle
sprouting angiogenesis
heart development
lymph vessel development
endothelium development
import across plasma membrane
ion transmembrane transport
Complement and coagulation cascades
response to methanol
S-adenosylhomocysteine metabolic process
cellular modified amino acid catabolic process
negative regulation of fatty acid metabolic process
response to hormone
Methylation
Propanoate metabolism
fatty acid beta-oxidation using acyl-CoA dehydrogenase
Fructose metabolism
histidine catabolic process
coenzyme A metabolic process
Taurine and hypotaurine metabolism
Pyruvate metabolism and Citric Acid (TCA) cycle
Arginine and proline metabolism
lipid homeostasis
Biosynthesis of unsaturated fatty acids
Glycerophospholipid metabolism
Selenocompound metabolism
protein homotetramerization
amino-acid betaine metabolic process
regulation of cholesterol metabolic process
aspartate family amino acid metabolic process
Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol
carbohydrate metabolic process
PPAR signaling pathway
sulfur compound biosynthetic process
Glycolysis / Gluconeogenesis
serine family amino acid catabolic process
pyruvate metabolic process
regulation of small molecule metabolic process
Pyruvate metabolism
Carbon metabolism
benzene-containing compound metabolic process
cellular ketone metabolic process
glutamine family amino acid metabolic process
sulfur amino acid metabolic process
Fatty acid degradation
glycosyl compound metabolic process
nucleotide biosynthetic process
organic hydroxy compound catabolic process
monocarboxylic acid biosynthetic process
sulfur compound catabolic process
response to toxic substance
Butanoate metabolism
one-carbon metabolic process
generation of precursor metabolites and energy
serine family amino acid metabolic process
aromatic amino acid family metabolic process
organic hydroxy compound metabolic process
organic cyclic compound catabolic process
Tryptophan metabolism
Glycine, serine and threonine metabolism
dicarboxylic acid metabolic process
cellular modified amino acid metabolic process
monocarboxylic acid metabolic process
sulfur compound metabolic process
small molecule biosynthetic process
carboxylic acid metabolic process
Vasculature development, Hippo signaling
Extracellular matrix, VEGF signaling
Metabolism related Terms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Legend
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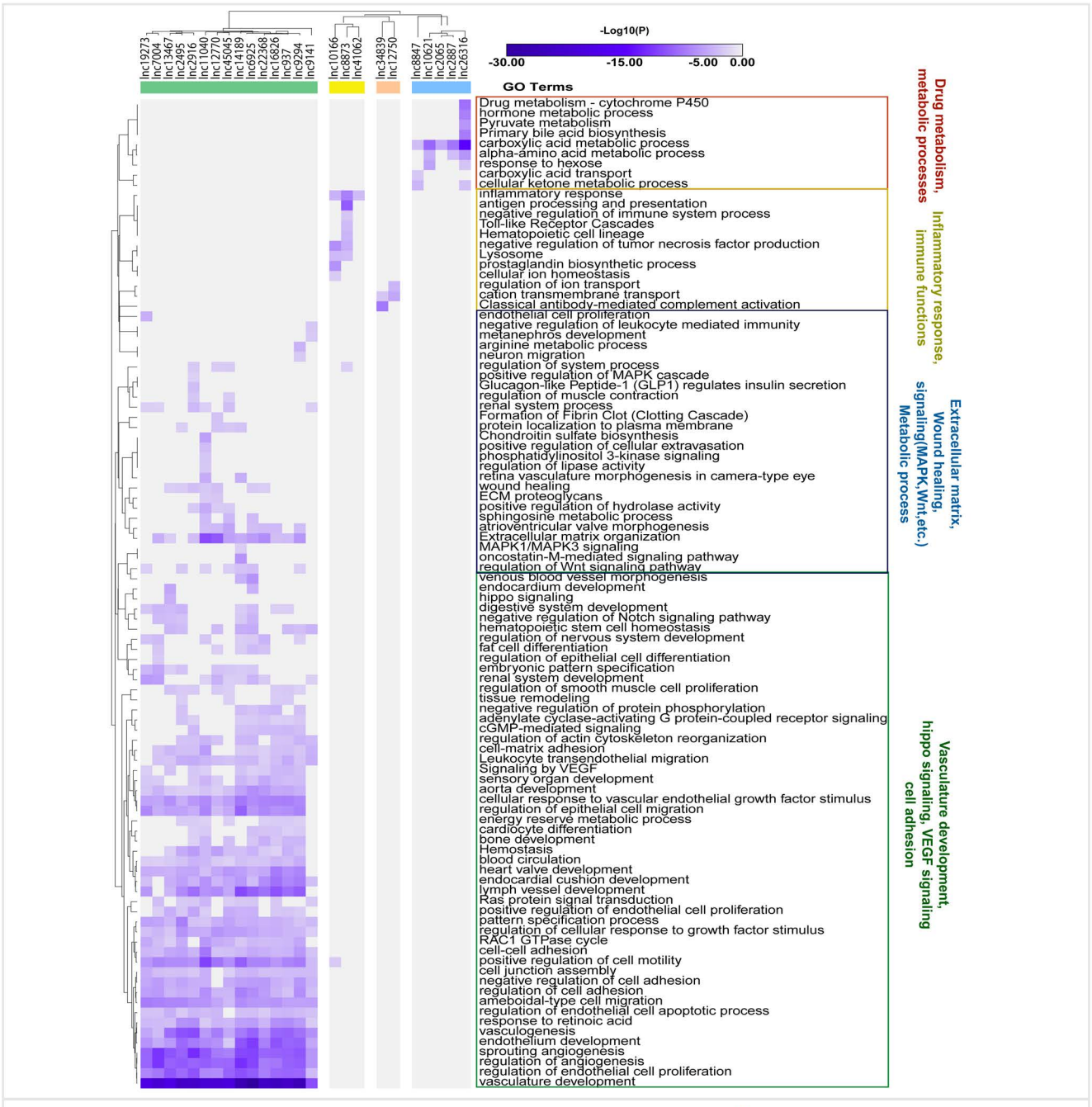
lncRNAs in cluster yellow
lncRNAs in cluster blue
PCG targets

Fig. S10 (NASH)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lnc8847
lnc10621
lnc2065
lnc2887
lnc26316
-Log10(P)
-30.00
-15.00
-5.00
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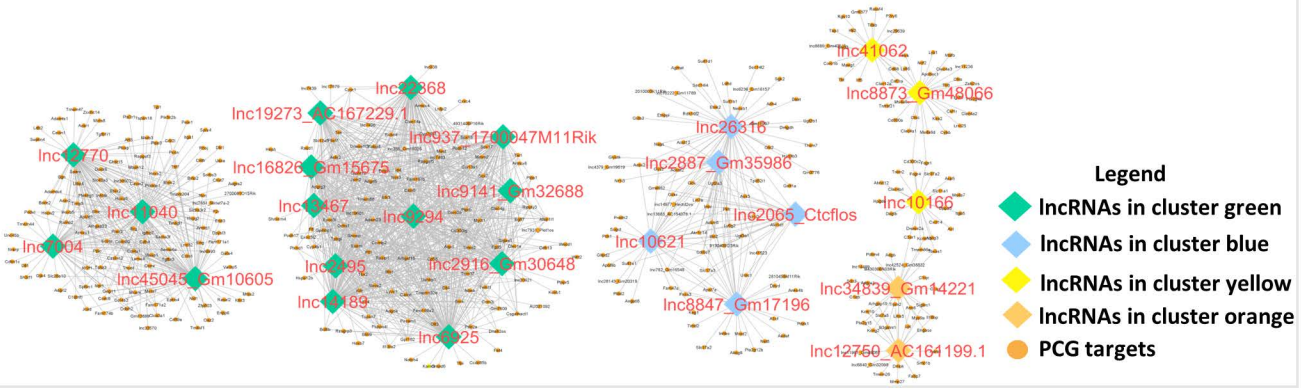
GO Terms
Drug metabolism - cytochrome P450
hormone metabolic process
Pyruvate metabolism
Primary bile acid biosynthesis
carboxylic acid metabolic process
alpha-amino acid metabolic process
response to hexose
carboxylic acid transport
cellular ketone metabolic process
inflammatory response
antigen processing and presentation
negative regulation of immune system process
Toll-like Receptor Cascades
Hematopoietic cell lineage
negative regulation of tumor necrosis factor production
Lysosome
prostaglandin biosynthetic process
cellular ion homeostasis
regulation of ion transport
cation transmembrane transport
Classical antibody-mediated complement activation
endothelial cell proliferation
negative regulation of leukocyte mediated immunity
metanephros development
arginine metabolic process
neuron migration
regulation of system process
positive regulation of MAPK cascade
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion
regulation of muscle contraction
renal system process
Formation of Fibrin Clot (Clotting Cascade)
protein localization to plasma membrane
Chondroitin sulfate biosynthesis
positive regulation of cellular extravasation
phosphatidylinositol 3-kinase signaling
regulation of lipase activity
retina vasculature morphogenesis in camera-type eye
wound healing
ECM proteoglycans
positive regulation of hydrolase activity
sphingosine metabolic process
atrioventricular valve morphogenesis
Extracellular matrix organization
MAPK1/MAPK3 signaling
oncostatin-M-mediated signaling pathway
regulation of Wnt signaling pathway
venous blood vessel morphogenesis
endocardium development
hippo signaling
digestive system development
negative regulation of Notch signaling pathway
hematopoietic stem cell homeostasis
regulation of nervous system development
fat cell differentiation
regulation of epithelial cell differentiation
embryonic pattern specification
renal system development
regulation of smooth muscle cell proliferation
tissue remodeling
negative regulation of protein phosphorylation
adenylate cyclase-activating G protein-coupled receptor signaling
cGMP-mediated signaling
regulation of actin cytoskeleton reorganization
cell-matrix adhesion
Leukocyte transendothelial migration
Signaling by VEGF
sensory organ development
aorta development
cellular response to vascular endothelial growth factor stimulus
regulation of epithelial cell migration
energy reserve metabolic process
cardiocyte differentiation
bone development
Hemostasis
blood circulation
heart valve development
endocardial cushion development
lymph vessel development
Ras protein signal transduction
positive regulation of endothelial cell proliferation
pattern specification process
regulation of cellular response to growth factor stimulus
RAC1 GTPase cycle
cell-cell adhesion
positive regulation of cell motility
cell junction assembly
negative regulation of cell adhesion
regulation of cell adhesion
ameboidal-type cell migration
regulation of endothelial cell apoptotic process
response to retinoic acid
vasculogenesis
endothelium development
sprouting angiogenesis
regulation of angiogenesis
regulation of endothelial cell proliferation
vasculature development
Drug metabolism, metabolic processes
Inflammatory response, immune functions
Extracellular matrix, Wound healing, signaling(MAPK,Wnt,etc.) Metabolic process
Vasculature development, hippo signaling, VEGF signaling cell adhesion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Legend
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lncRNAs in cluster blue
lncRNAs in cluster yellow
lncRNAs in cluster orange
PCG targets

Fig. S11 (Chow-NAFLD-NASH)

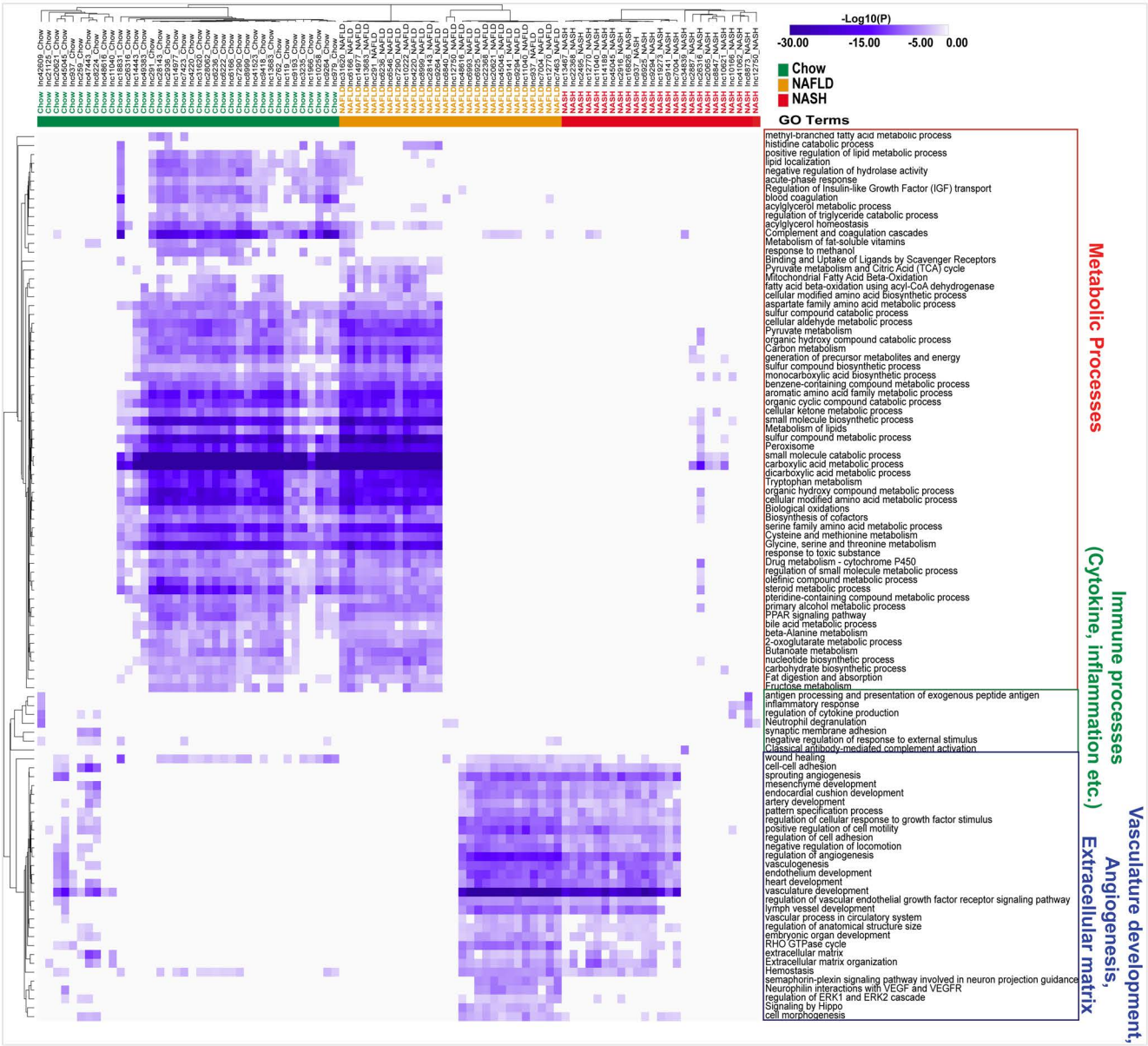
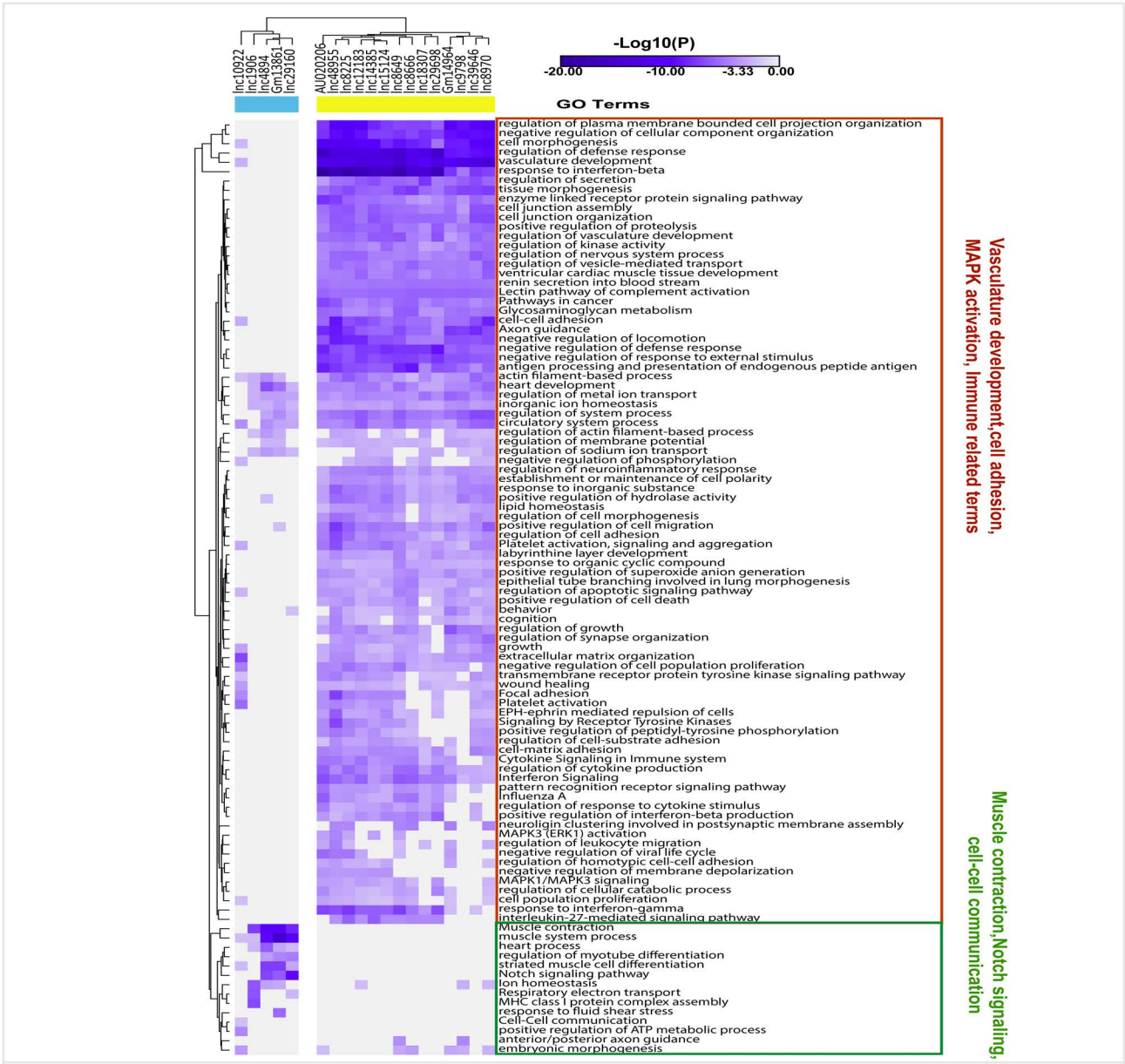


Fig. S12
(Healthy mesenchyme)



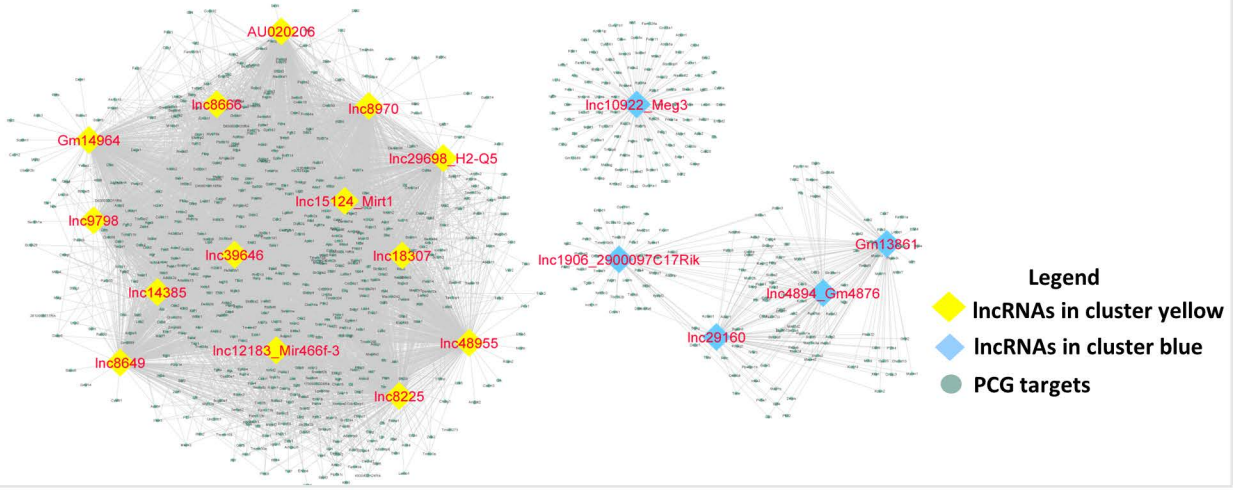


Fig. S13
(CCl_4 mesenchyme)

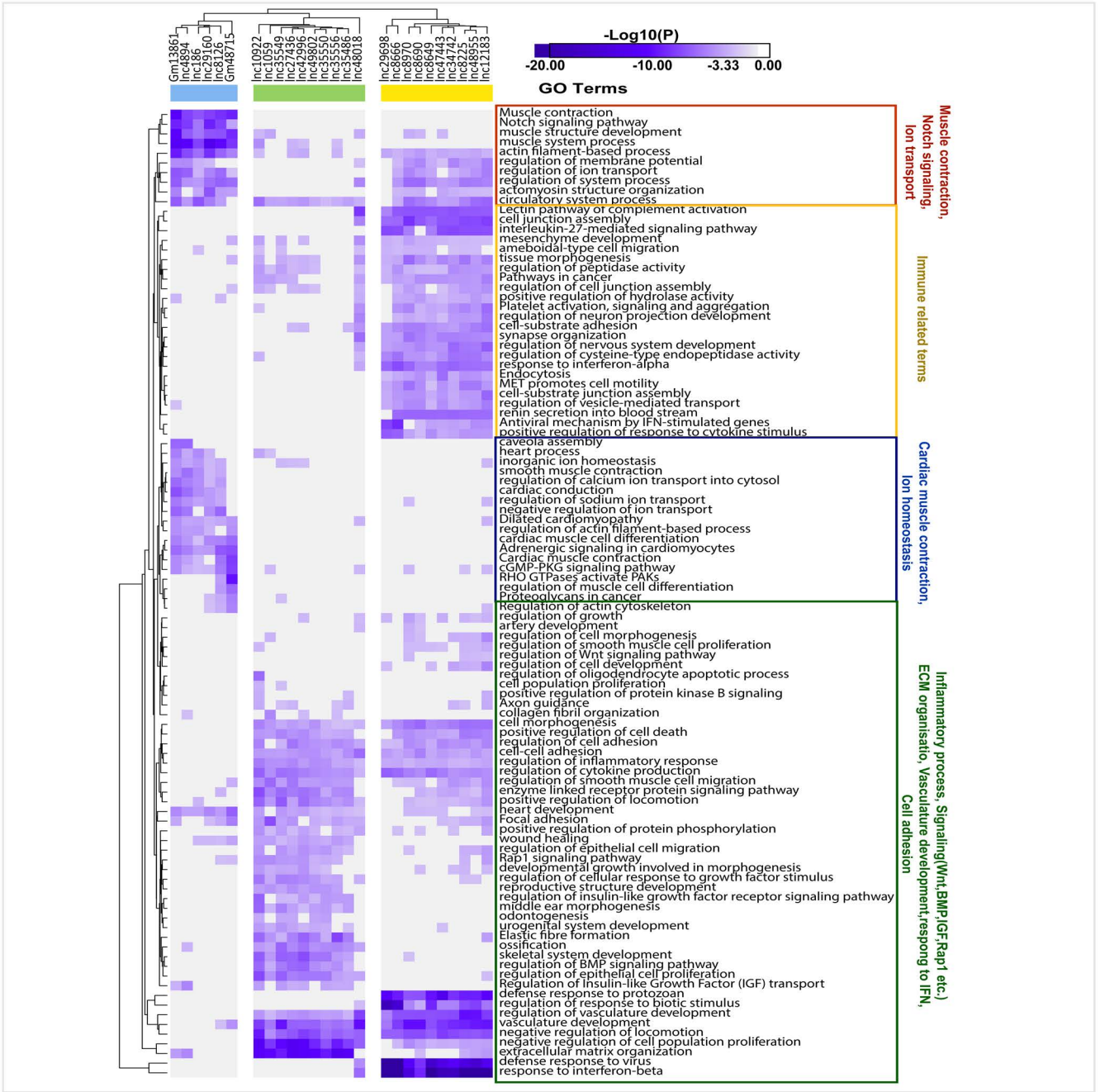


Fig. S14
(Healthy-CCl_4 mesenchyme)

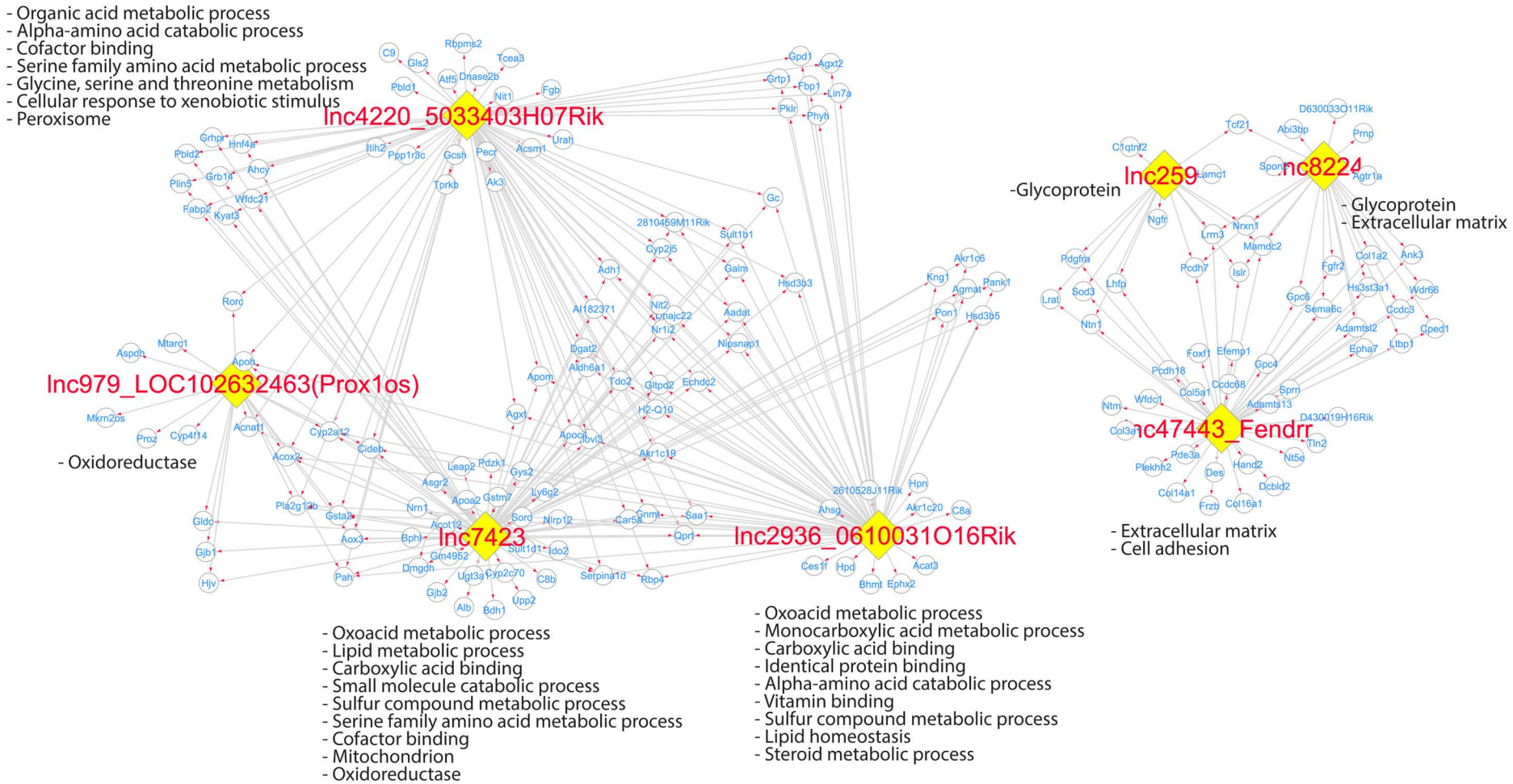


Fig. S15A (Chow)

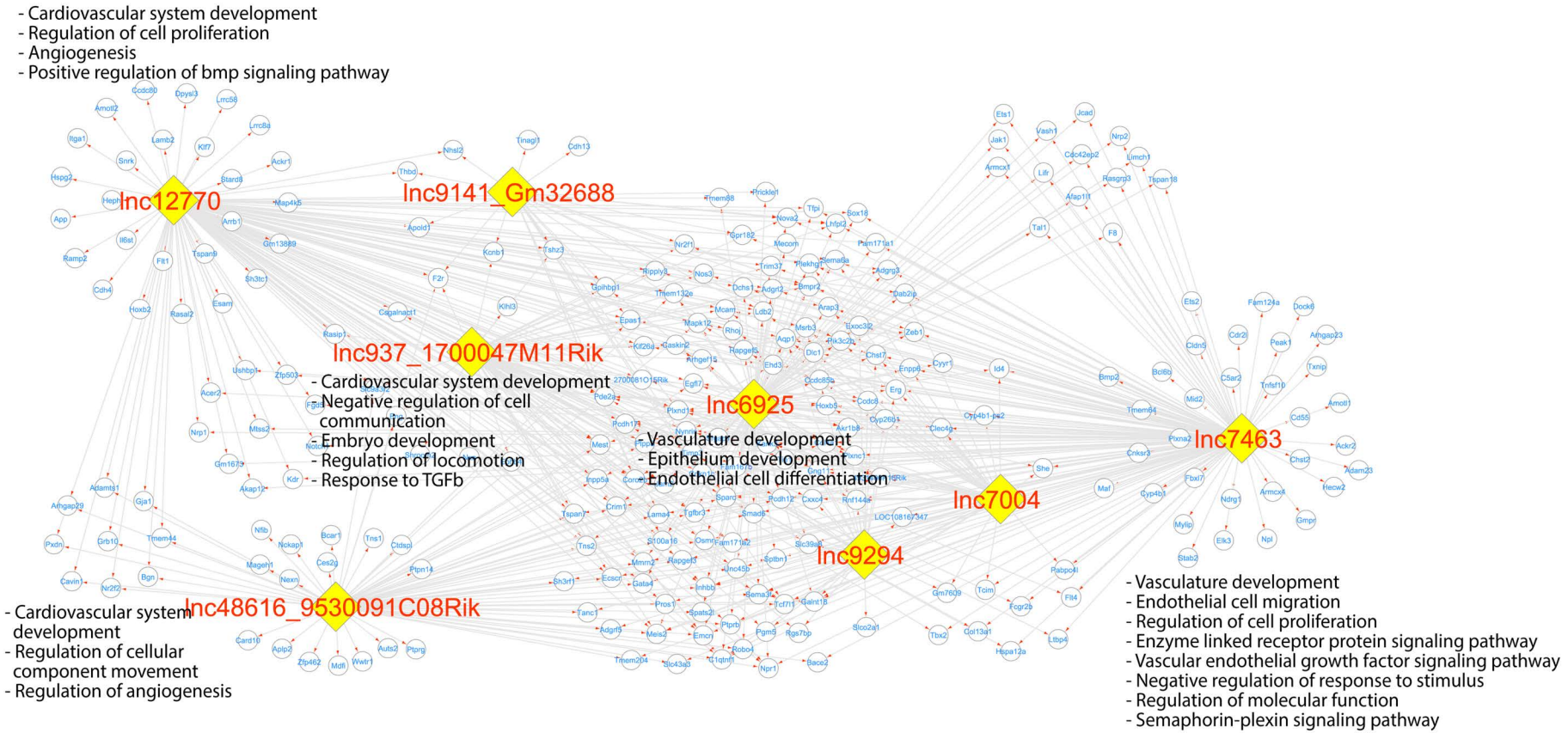


Fig. S15B (NAFLD)

Fig. S15C (NASH)

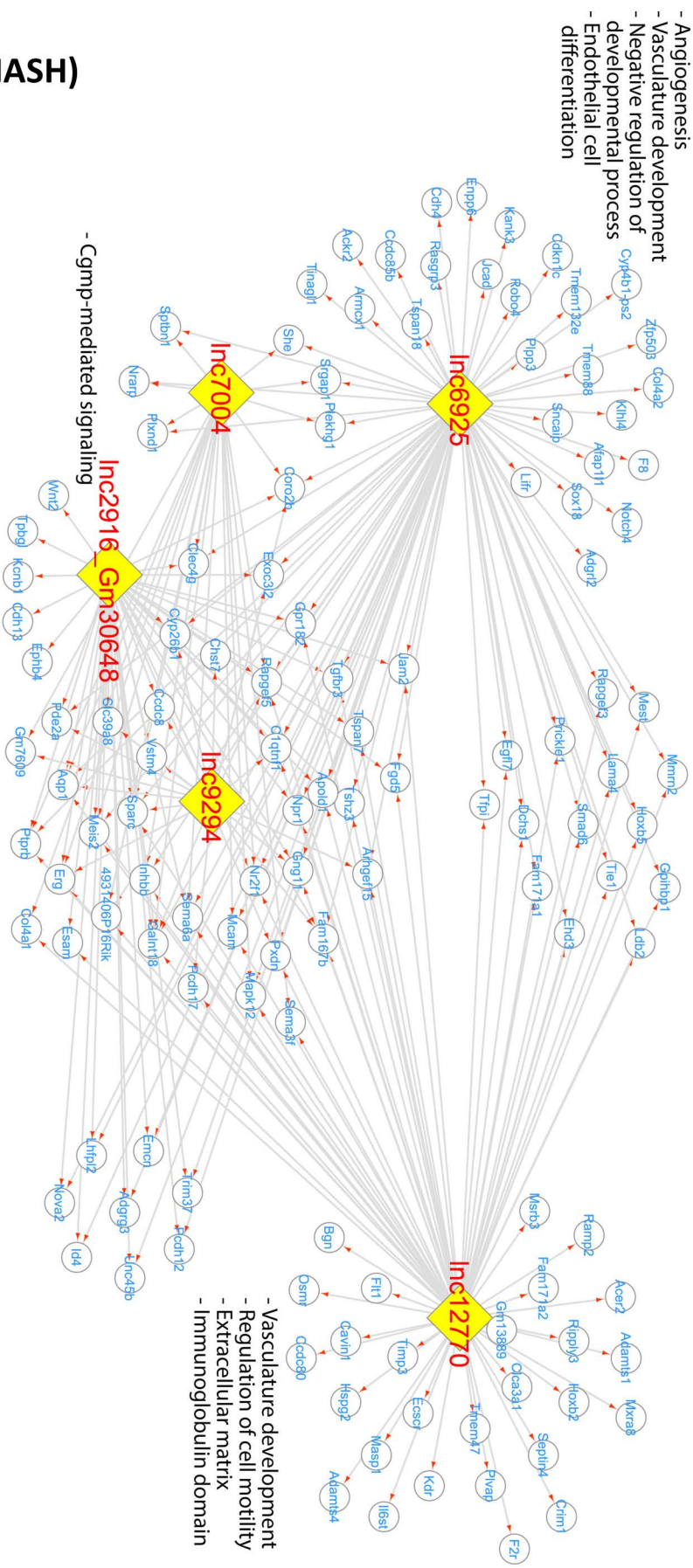


Fig. S16A
(Healthy Mesenchyme)

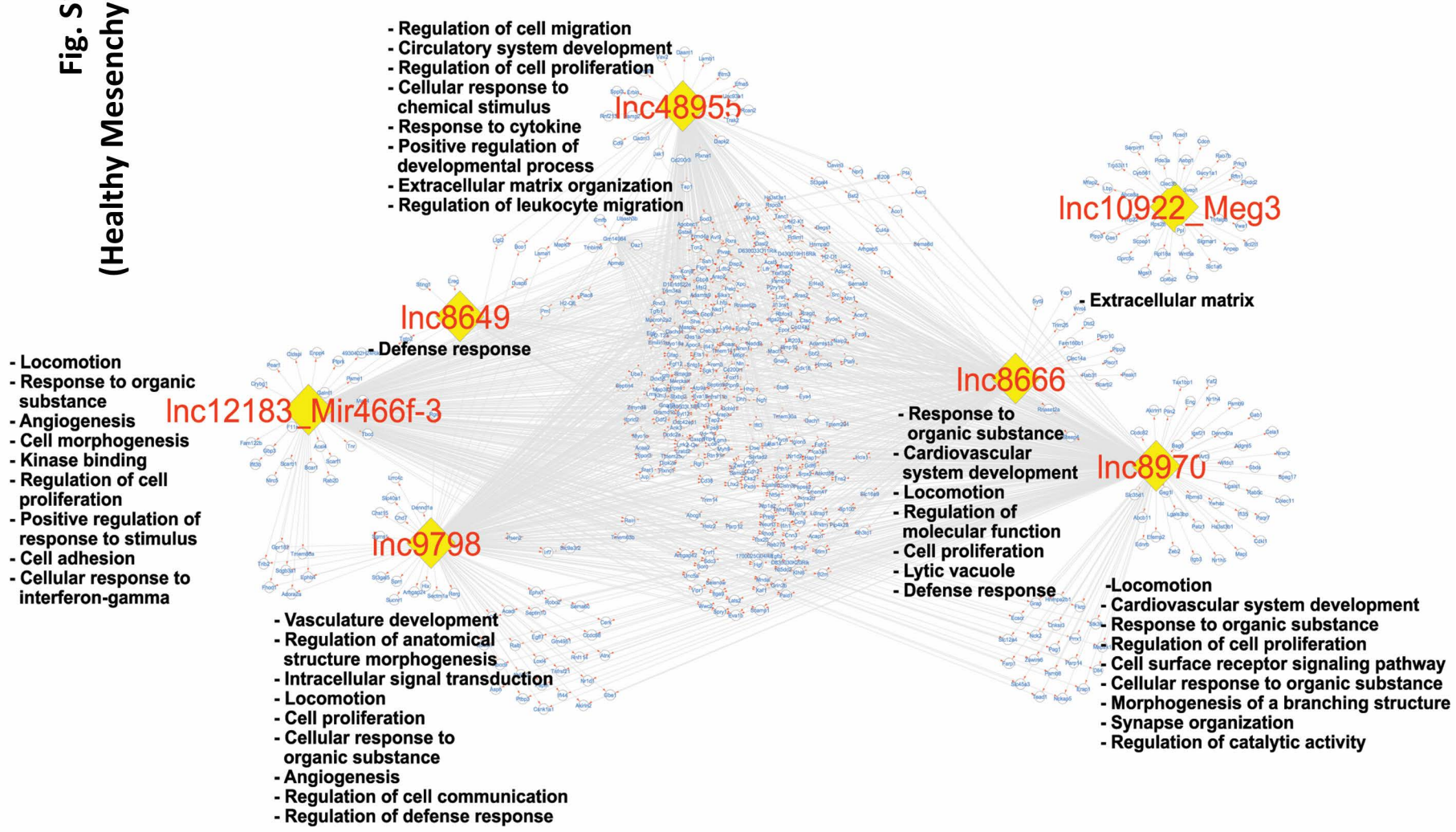


Fig. S16B
(CCl_4 Mesenchyme)

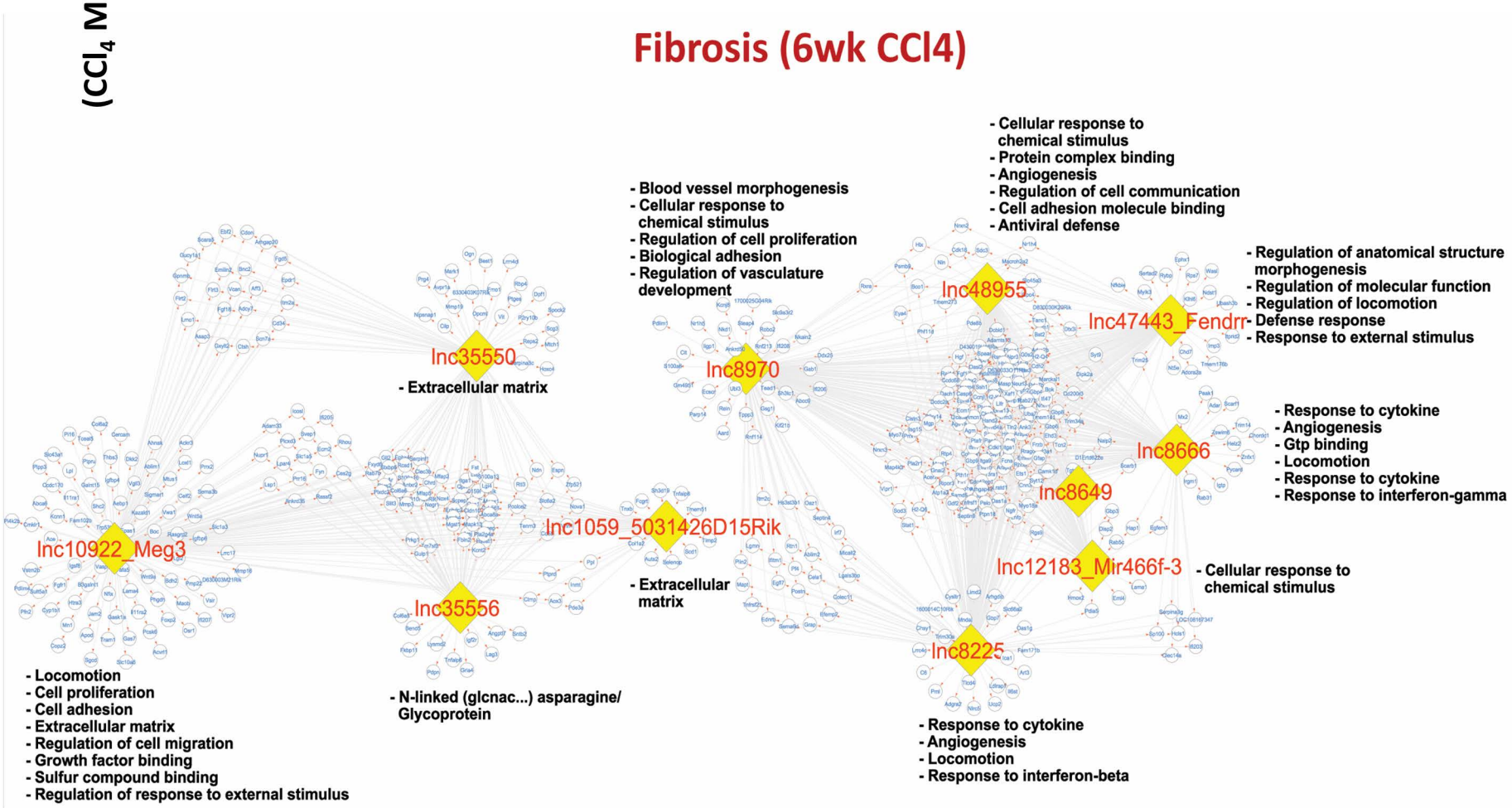
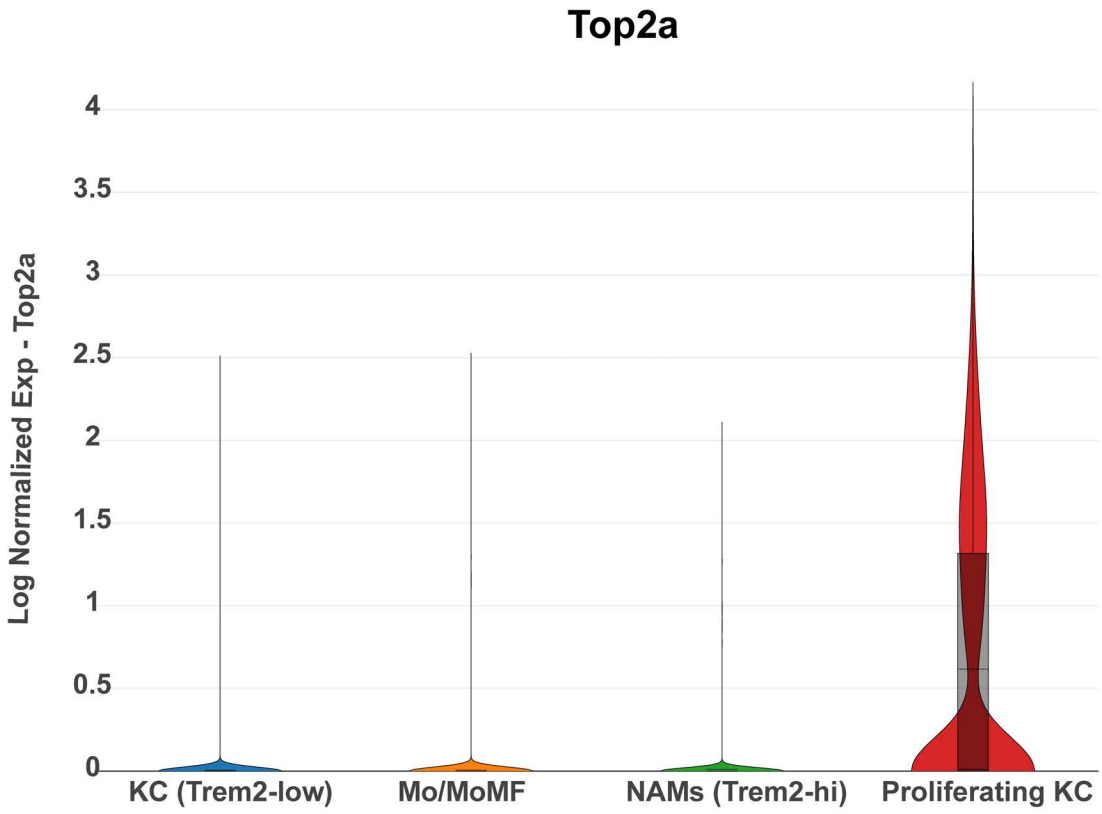


Fig. S17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3
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2
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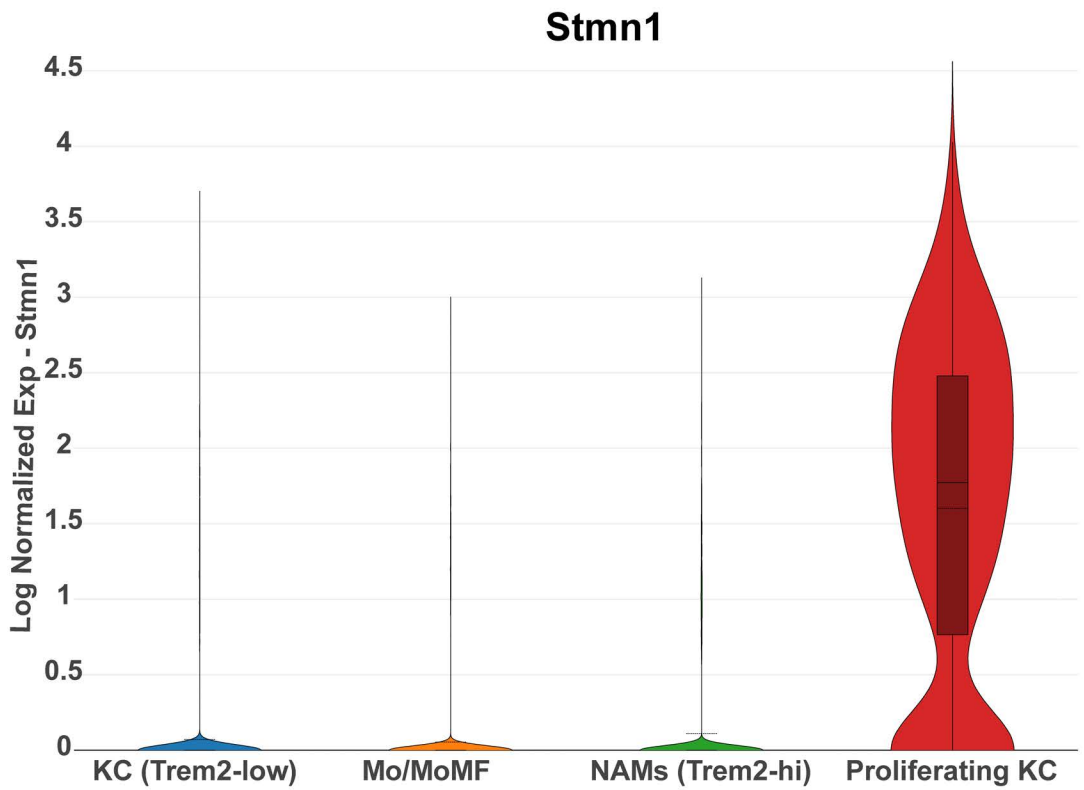
Mo/MoMF
NAMs (Trem2-hi)
Proliferating KC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1
0.5
0
KC (Trem2-low)
Mo/MoMF
NAMs (Trem2-hi)
Proliferating KC