miRNA/mRNA signature of mouse Kupffer cells during the progression of chronic liver disease from fibrosis to hepatocellular carcinoma

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Introduction

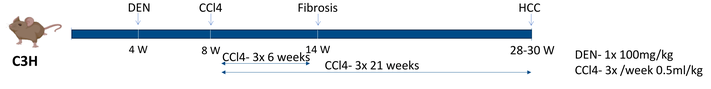
Immune dysregulation is an important factor for chronic liver disease (CLD) progression from fibrosis to hepatocellular carcinoma (HCC), with Kupffer cells (KCs) playing a pivotal role. KCs are liver resident macrophages that form the primary line of defence in liver. An imbalance in the hepatic macrophage population becomes evident during CLD progression from liver fibrosis to HCC.

Aim

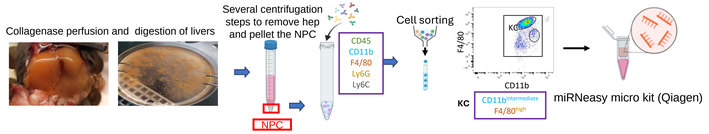
This study aims to explore the differentially expressed (DE) miRNA and mRNA profiles in mouse KCs to identify the key molecular mechanisms driving liver fibrosis and HCC.

Method

1. Mice models



2. KC sorting and RNA extraction



3. DE Genes and miRNA–mRNA Interactions :

Enriched pathways and genesets were identified according to GOBP and KEGG results. Predicted miRNA targets from TargetScan and DIANA-microT-CDS were matched with inversely expressed mRNAs from our DEmRNA data. Key miRNA–mRNA pairs logFC > 1 or logFC < -1, padj < 0.05 were used to identify enriched pathways and regulatory networks.

Conclusions

- We observed that in both Fibrosis and HCC, dysregulation of immune regulation, ion transport, collagen biogenesis and extracellular matrix remodelling, signalling pathways, angiogenesis and epithelial mesenchymal transition occurs in KCs.
- We associate downregulation of miR-29c-3p in KCs during HCC to be important for extracellular matrix reorganisation, TGF-β signaling and epithelial mesenchymal transition- promoting tumor development.

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Results

Figure 1: Number of upregulated and downregulated genes in both conditions with | logFC | > 1 or | logFC | < -1, padj < 0.05

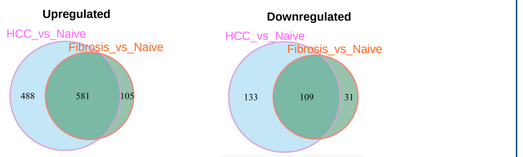
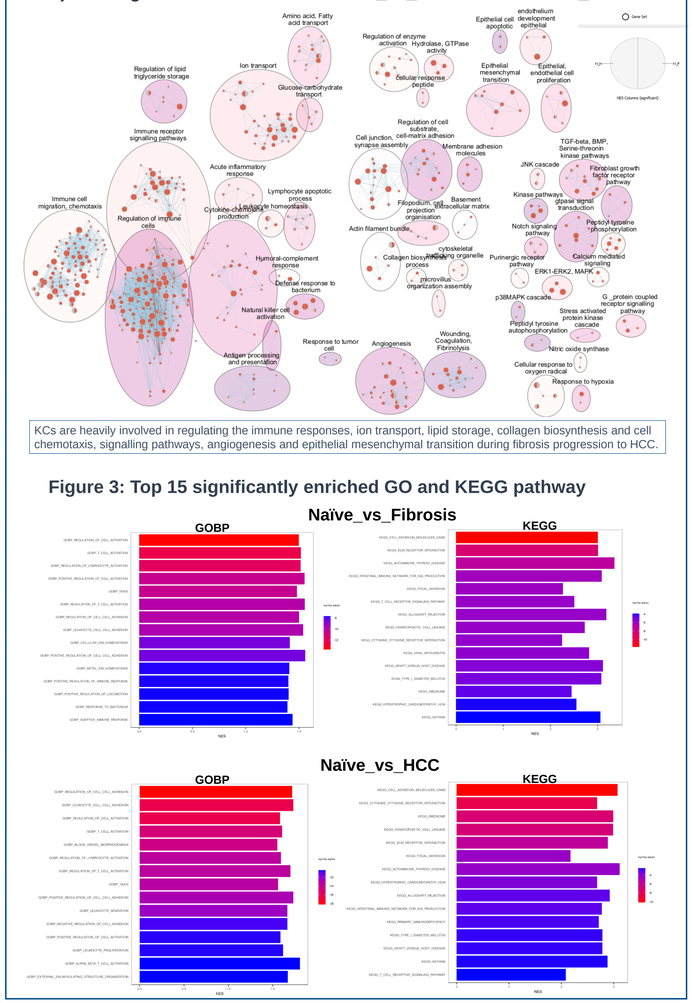


Figure 2: Geneset enrichment analysis showing significantly enriched (FDR <0.05) GOBP genesets of interest in Naïve_vs_Fibrosis and Naïve_vs HCC



KCs are heavily involved in regulating the immune responses, ion transport, lipid storage, collagen biosynthesis and cell chemotaxis, signalling pathways, angiogenesis and epithelial mesenchymal transition during fibrosis progression to HCC.

Figure 3: Top 15 significantly enriched GO and KEGG pathway

Figure 4: a) Significant DEmiRNAs and their target genes b) miRNA-target mRNA network c) Significantly enriched pathway in Naïve_vs_Fibrosis group

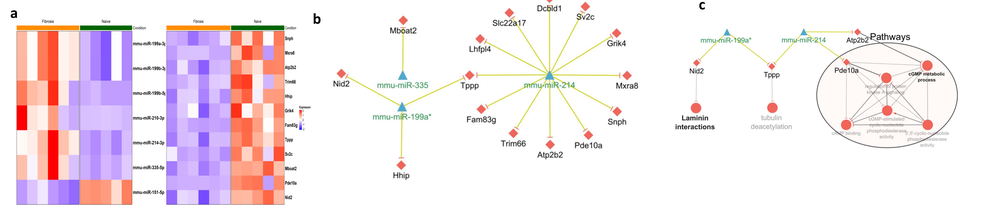
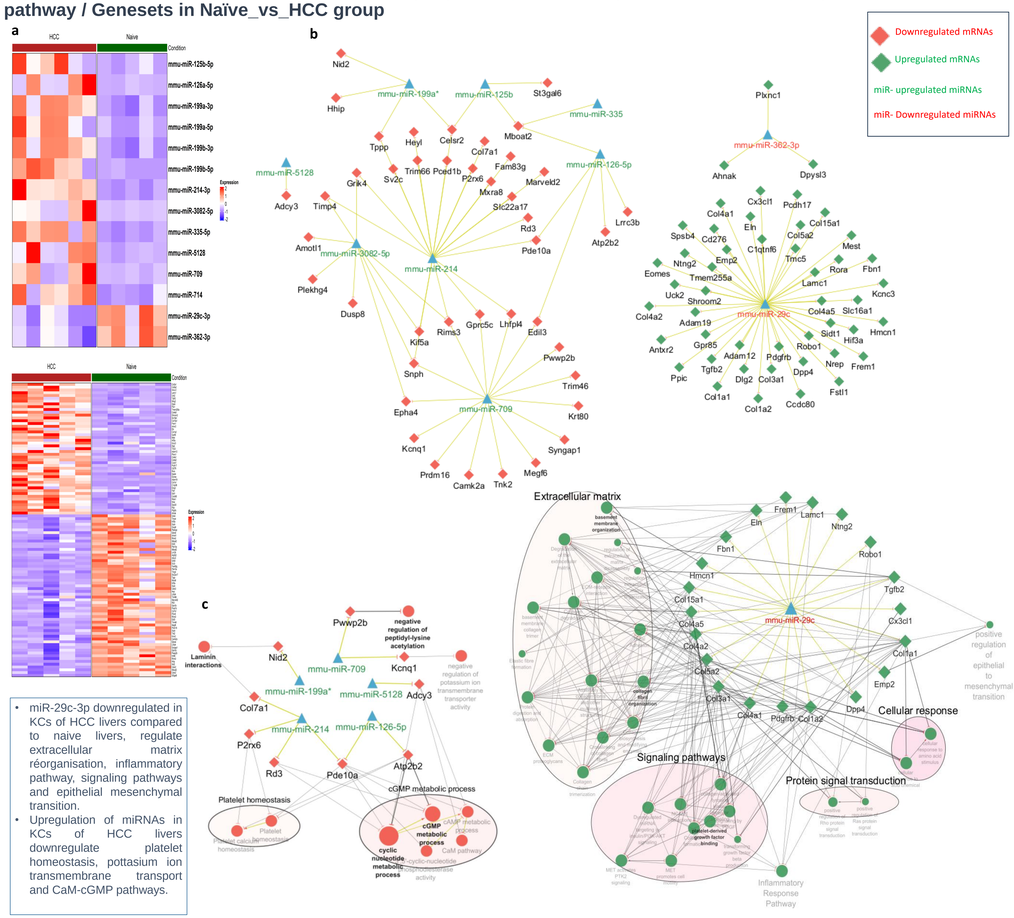


Figure 5: a) Significant DEmiRNAs and their target genes b) miRNA-target mRNA network c) Significantly enriched pathway / Genesets in Naïve_vs_HCC group



- miR-29c-3p downregulated in KCs of HCC livers compared to naive livers, regulate extracellular matrix réorganisation, inflammatory pathway, signaling pathways and epithelial mesenchymal transition.
- Upregulation of miRNAs in KCs of HCC livers downregulate platelet homeostasis, pottasium ion transmembrane transport and CaM-cGMP pathways.