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LIVER

Spatial division of hepatic metabolic labour

A remarkable feature of the liver is zonation, which refers to the spatial allocation of key metabolic pathways to distinct layers within liver lobules. However, technological limitations have hindered the genome-wide annotation of zonation. Now, a study published in *Nature* provides further insight into this spatial distribution of metabolic genes, which was achieved through a global transcriptome-based reconstruction of zonation at single-cell resolution in the mouse liver. "We felt that solving the global spatial division of labour would provide new insights into liver heterogeneity and the design principles of this tissue," explains author Shalev Itzkovitz.

To obtain zonation profiles, the researchers devised a novel method to measure global gene expression signatures in mouse hepatocytes and determine their precise lobule coordinates. The team generated a spatial atlas of key zonated liver genes using single-molecule fluorescence *in situ* hybridization (smFISH), and used single-cell RNA sequencing (scRNA-seq) technology to measure the transcriptome of thousands of liver cells. "We developed an algorithm that combines these two datasets (scRNA-seq and our smFISH spatial atlas) to deduce the original lobule coordinate of each of the sequenced cells," explains Itzkovitz.

The investigators succeeded in obtaining a global zonation profile at high spatial resolution in hepatocytes spanning the portocentral lobule axis. A key finding was that ~50% of the ~7,000 genes expressed in hepatocytes were markedly zonated. In addition, the investigators found that key liver genes were distinctly expressed in the mid-lobule layers, including *Hamp* and *Hamp2* (which encode the iron-regulatory protein hepcidin), and insulin-like growth factor binding protein 2 (*Igfbp2*). This discovery challenges the traditional binary classification of the liver into periportal and pericentral zones, and reveals that the intermediate lobule might be more functionally specialized than previously appreciated.

The study also revealed that the spatial order and expression of key metabolic genes matched their position in their respective enzymatic cascades. Important genes in the bile acid biosynthesis pathway were differentially expressed between lobule layers, which coincides with the flow of bile and challenges the previous stance that this process was exclusively pericentral.

"It seems that there are distinct subtypes of hepatocytes defined by their radial coordinates, fundamentally differing in their entire gene expression signatures," notes Itzkovitz. Whether these spatially graded hepatocytes differ only by their metabolic input or are distinct cell types is a key question that requires further research. This novel approach could be applied to decode spatial genetic profiles in other organs, such as the intestinal villus, and could provide new insights into various pathological liver states.

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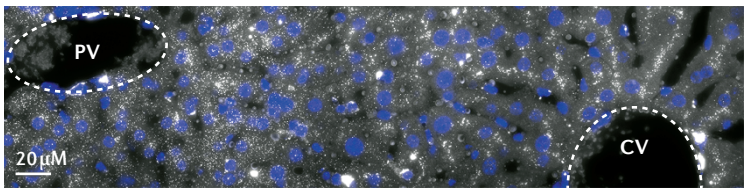

Periportal zonation of *Acly*, encoding the enzyme ATP citrate lyase. Bright dots are individual mRNA molecules of *Acly*, blue are DAPI stained nuclei. PV, portal vein; CV, central vein. Image courtesy of S. Itzkovitz, Weizmann Institute of Science, Israel.

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