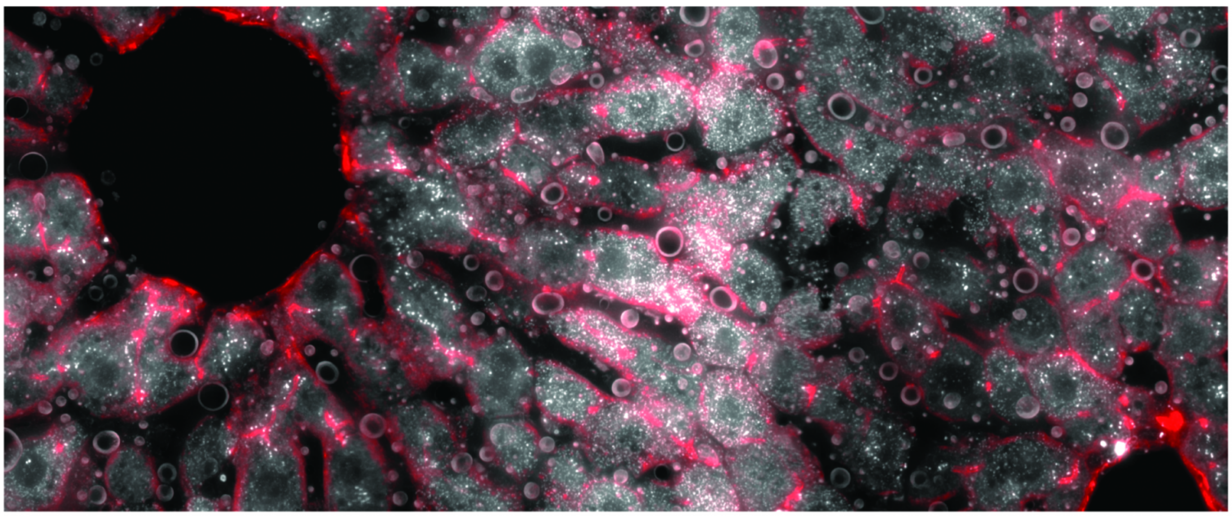
Gene analysis adds layers to understanding how our livers function

April 10 2017



Cross section of a mouse liver lobule under a fluorescence microscope. The middle layer reveals an abundance of messenger RNA molecules (white dots) for the gene encoding hepcidin, the iron-regulating hormone Credit: Weizmann Institute of Science

If you get up in the morning feeling energetic and clearheaded, you can thank your liver for manufacturing glucose before breakfast time. Among a host of other vital functions, it also clears our body of toxins and produces most of the carrier proteins in our blood. In a study reported recently in *Nature*, Weizmann Institute of Science researchers showed that the liver's amazing multitasking capacity is due at least in part to a clever division of labor among its cells.

Each of the liver's microscopic, hexagonal lobules consists of onion-like concentric layers. By mapping gene activity in all the cells of a liver lobule, Dr. Shalev Itzkovitz of Weizmann's Molecular Cell Biology Department and his research team have revealed that these layers each perform different functions. Itzkovitz says: "We've found that liver cells can be divided into at least nine different types, each specializing in its own tasks."

The scientists found, for instance, that the synthesis of glucose, blood-clotting factors and various other materials takes place in the outer layers of the liver lobule. "These layers are rich in the oxygen needed to fuel these costly synthesis processes," explains Itzkovitz.

The inner layers of the liver lobules revealed themselves to be the sites where toxins and other substances are broken down. The middle layers also proved to have their own functions, rather than serving as mere transition zones: The researchers found, for example, that cells in these layers manufacture the hormone hepcidin, which regulates iron levels in the blood.

The scientists also discovered that certain processes, such as the manufacture of bile, proceed across several different layers, in something like a production line.

These discoveries emerged when the researchers created a spatial atlas of gene expression for all liver cells, the first of its kind for this organ. In collaboration with Prof. Ido Amit of Weizmann's Immunology Department, they analyzed the genomes of 1,500 individual liver cells, establishing patterns of expression for about 20,000 genes in each cell. In parallel they visualized intact liver tissue, locating individual messenger RNA molecules under a fluorescence microscope, using a method developed by Itzkovitz and his colleagues. Special algorithms then enabled the researchers to establish both the gene expression in each cell and the location of these cells in the liver lobule. They found that more than half of the 7,000 genes expressed in the liver vary in activity from one layer to another, a number that is about ten times greater than previous estimates.

Such an in-depth analysis of gene expression may help clarify the course and origin of common liver disorders, including liver cancer and non-alcoholic fatty liver disease, which affects about a fifth of the population in developed countries. In addition the approach developed in the new study may now be applied to map gene expression elsewhere in the body.

More information: Keren Bahar Halpern et al. Single-cell spatial reconstruction reveals global division of labour in the mammalian liver, *Nature* (2017). DOI: 10.1038/nature21065

Provided by Weizmann Institute of Science