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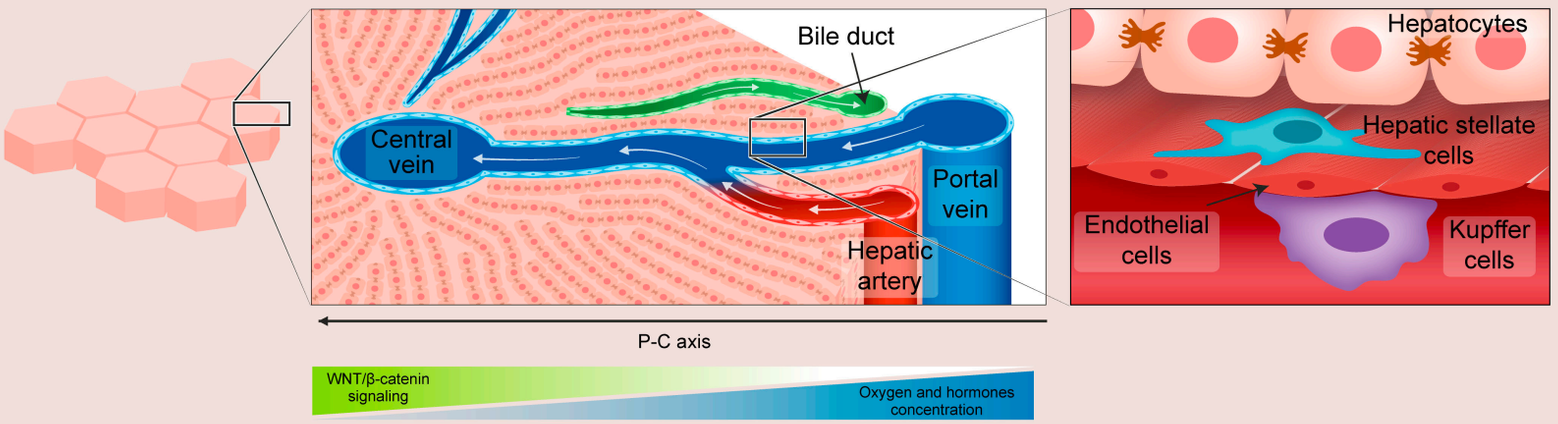
Hepatology Snapshot:

Liver zonation

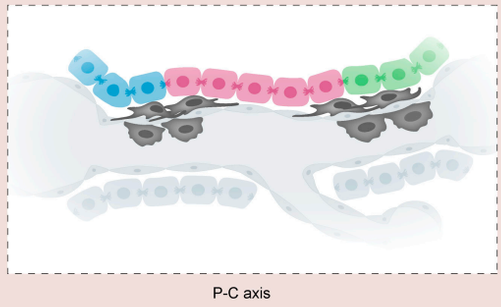
Rita Manco[1], Shalev Itzkovitz[1,*]

[1]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel
*Corresponding author. Address: Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 7610001, Israel; Tel.: +972-8-934-3104, fax: +972-8-934-4125.
E-mail address: shalev.itzkovitz@weizmann.ac.il (S. Itzkovitz).

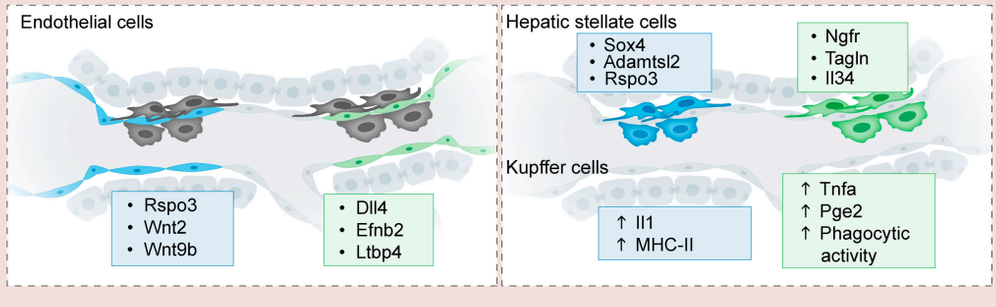
A Liver microanatomy - the liver lobule



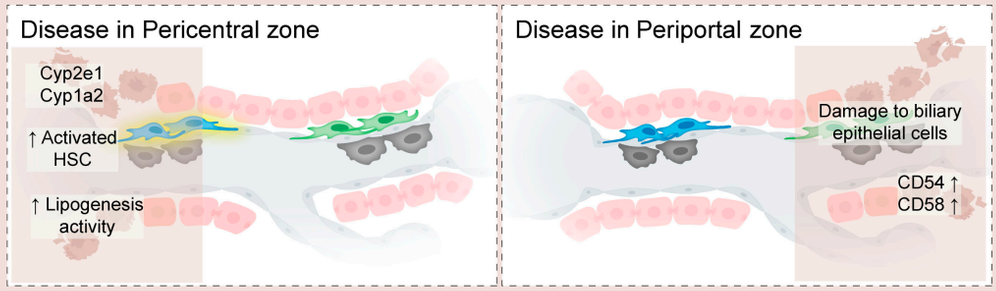
B Hepatocyte zonation



C NPC zonation



D Zonation in disease



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The liver is a central organ that preserves physiological homeostasis. It is a highly structured organ composed of hexagonal-shaped anatomical units termed 'liver lobules'. Blood rich in oxygen enters the liver lobule at peripheral portal tracts and drains out through the central vein. Conversely, bile flows outwards from the lobule centres and drains out through portal bile ducts.[1] Hepatocytes, the main liver cell type, are arranged in hepatic plates that extend radially along the lobule axis. At the basolateral domains, hepatocytes face fenestrated endothelial cells that form the radial sinusoidal blood vessels. Hepatic stellate cells (HSCs), vitamin A storing cells that can become extracellular matrix producers, reside in the "space of Disse" between hepatocytes and the sinusoids. Kupffer cells (KCs), the liver resident macrophages, are largely immotile cells residing within the sinusoids. As blood flows inwards, hepatocytes take up and secrete nutrients and sense hormones (insulin, glucagon, growth and thyroid hormones). Sequential hepatocyte consumption and production, together with local tissue morphogens, give rise to a graded microenvironment. In line with these gradients, liver functions are non-uniformly distributed along the lobule radial axis, a phenomenon that has been termed "liver zonation".[2,3]

Hepatocyte zonation patterns seem to optimize overall liver function, in the face of structural constraints.[4] Processes that are energetically demanding, such as protein secretion and gluconeogenesis, are allocated to the portal layers, where oxygen is more abundant. Mid-lobule hepatocytes specialize in the secretion of the iron-regulating hormone hepcidin, among other tasks. Pericentral hepatocytes preferentially engage in xenobiotic metabolism, bile acid biosynthesis and glycolysis, which are less energetically demanding processes.[4,5] Some zonated processes exhibit spatial recycling of material. An example is the urea cycle, where periportal hepatocytes detoxify ammonia to generate urea, a task that requires the breakdown of glutamine into glutamate.[1] Pericentral hepatocytes, in turn, take up the excess glutamate and reconvert it to glutamine, thus maintaining amino acid balance at the entries and exits of the lobule. Additional examples of opposite zonated tasks include periportal production and pericentral uptake of glucose, as well as periportal cholesterol biosynthesis and pericentral cholesterol consumption. Some pathways, such as the neutral bile acid biosynthesis cascade, follow 'production line' patterns, whereby sequential enzymes in the cascade are expressed in sequential lobule layers.[4,5] Of note, there are discrepancies between human and mouse zonation.[6]

The Wnt pathway stands out as a major regulator of hepatic zonation, as about a third of hepatic zonated genes are Wnt targets.[3] The pericentral liver endothelial cells are a source of key Wnt-pathway ligands such as *Wnt2*, *Wnt9b and Rspo3,*[7] the latter also expressed by pericentral HSCs.[8] Pericentral HSCs further express elevated levels of *Sox4* and *Adamtsl2,* whereas periportal HSCs exhibit zonated expression of *Ngfr, Il34* and *Tagln*.[8] Periportal KCs are more abundant, larger and exhibit higher phagocytic activity compared to pericentral KCs.[9] Periportal KCs produce more *Tnfα* and *Pge2*, while pericentral KCs produce more *Il-1*.[9]

Liver zonation can explain zonated damage in liver pathology. The zonated processes of xenobiotic metabolism lead to pericentral damage upon overdoses of drugs such as acetaminophen. This is due to the accumulation of toxic intermediates exclusively in the hepatocytes that express the detoxification machinery, especially *Cyp2e1* and *Cyp1a2*.[10] Pericentral injury is also associated with the activation of pericentral HSCs.[7] The development of non-alcoholic and alcohol-related liver diseases mostly begins in the pericentral zone as well, potentially linked to its higher lipogenic activity.[5] Periportal damage is observed in autoimmune hepatitis, in part due to the zonated expression of antigens such as CD54 and CD58,[11] and in biliary diseases, due to the damage to epithelial cells that form the periportal bile duct.[5]

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Conflict of interest

The authors declare no competing personal or financial interests.

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Authors' contributions

Both authors wrote the paper.

Data availability statement

Data are available online.

Supplementary data

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Author names in bold designate shared co-first authorship

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