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Letter to the editor:

LIVER FIBROSIS CAUSES PERIPORTALIZATION OF LOBULAR ZONATION

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Dear Editor,

The human liver consists of approximately one million liver lobules, which are known to show metabolic zonation (Braeuning et al., 2006; Halpern et al., 2017; Saito et al., 2013). Zonation is the spatial separation of different metabolic pathways along the porto-central axis of the liver lobule (Gebhardt and Matz-Soja, 2014; Kietzmann, 2019; Godoy et al., 2013). For example, many phase-I-metabolizing enzymes are located in the center of the liver lobule (Schenk et al., 2017; Sezgin et al., 2018; Ghallab, 2017). The advantage of this arrangement is that many xenobiotics are detoxified before they are drained into the central vein and reach the general circulation (Hewitt et al., 2007; Bartl et al., 2015; Schliess et al., 2014). However, some compounds are metabolically activated by pericentrally expressed liver enzymes (Gebhardt et al., 2003; Bolt, 2017; Hengstler et al., 2000). This leads to a pericentral pattern of necrosis induced by many hepatotoxic compounds that require metabolic activation (Hammad et al., 2017; Hoehme et al., 2007; 2010).

Liver fibrosis is caused by chronic liver damage that leads to inflammation and scarring (Pimpin et al., 2018; Weiskirchen and Tacke, 2016; Gressner and Weiskirchen, 2006; Leist et al., 2017). Currently, little is known how liver fibrosis influences lobular zonation. In a recent issue of Cells, a study has been published, demonstrating that liver fibrosis causes 'periportalization' of lobular zonation (Ghallab et al., 2019). Periportalization means that the entire liver lobule adopts a periportal gene expression pattern, including the pericentral zone. To study this phenomenon, RNA-sequencing data were generated using fibrotic livers of mice caused by repeated CCl_4 administration (Ghallab et al., 2019). Interestingly, pericentral genes were enriched among genes downregulated by CCl_4, while periportal genes were enriched among the upregulated genes. This pattern of periportalization was confirmed by immunostaining. It also occurred when liver fibrosis was induced by a mouse model of obstructive cholestasis (Ghallab et al., 2019). The advantage of a periportalized lobular zonation is that hepatotoxic xenobiotics that require metabolic activation by cytochrome P450 enzymes cause less damage to the liver. This has been shown by the authors using the example of acetaminophen (Ghallab et al., 2019). However, this advantage is obtained at the expense of suboptimal fine-tuning of physiological metabolic functions, e.g. detoxification of ammonia (Ghallab et al., 2016). It will be interesting to learn in future, whether periportalization of lobular zonation demonstrated in fibrotic mouse livers also occurs in human liver fibrosis.

Conflict of interest

The author declares no conflict of interest.

REFERENCES

Bartl M, Pfaff M, Ghallab A, Driesch D, Henkel SG, Hengstler JG, et al. Optimality in the zonation of ammonia detoxification in rodent liver. Arch Toxicol. 2015;89:2069-78. doi: 10.1007/s00204-015-1596-4.

Bolt HM. Highlight report: The pseudolobule in liver fibrosis. EXCLI J. 2017;16:1321-2. doi: 10.17179/excli2017-1038.

Braeuning A, Ittrich C, Köhle C, Hailfinger S, Bonin M, Buchmann A, et al. Differential gene expression in periportal and perivenous mouse hepatocytes. FEBS J. 2006;273:5051-61.

Gebhardt R, Hengstler JG, Müller D, Glöckner R, Buenning P, Laube B, et al. New hepatocyte in vitro systems for drug metabolism: metabolic capacity and recommendations for application in basic research and drug development, standard operation procedures. Drug Metab Rev. 2003;35:145-213.

Gebhardt R, Matz-Soja M. Liver zonation: Novel aspects of its regulation and its impact on homeostasis. World J Gastroenterol. 2014;20:8491-504. doi: 10.3748/wjg.v20.i26.8491.

Ghallab A. Highlight report: Metabolomics in hepatotoxicity testing. EXCLI J. 2017;16:1323-5. doi: 10.17179/excli2017-1041.

Ghallab A, Cellière G, Henkel SG, Driesch D, Hoehme S, Hofmann U, et al. Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases. J Hepatol. 2016;64:860-71. doi: 10.1016/j.jhep.2015.11.018.

Ghallab A, Myllys M, Holland CH, Zaza A, Murad W, Hassan R, et al. Influence of liver fibrosis on lobular zonation. Cells. 2019;8:E1556. doi: 10.3390/cells8121556.

Godoy P, Hewitt NJ, Albrecht U, Andersen ME, Ansari N, Bhattacharya S, et al. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. Arch Toxicol. 2013;87:1315-530. doi: 10.1007/s00204-013-1078-5.

Gressner AM, Weiskirchen R. Modern pathogenetic concepts of liver fibrosis suggest stellate cells and TGF-beta as major players and therapeutic targets. J Cell Mol Med. 2006;10:76-99.

Halpern KB, Shenhav R, Matcovitch-Natan O, Toth B, Lemze D, Golan M, et al. Single-cell spatial reconstruction reveals global division of labour in the mammalian liver. Nature. 2017;542:352-6. doi: 10.1038/nature21065.

Hammad S, Braeuning A, Meyer C, Mohamed FEZA, Hengstler JG, Dooley S. A frequent misinterpretation in current research on liver fibrosis: the vessel in the center of CCl4-induced pseudolobules is a portal vein. Arch Toxicol. 2017;91:3689-92. doi: 10.1007/s00204-017-2040-8.

Hengstler JG, Utesch D, Steinberg P, Platt KL, Diener B, Ringel M, et al. Cryopreserved primary hepatocytes as a constantly available in vitro model for the evaluation of human and animal drug metabolism and enzyme induction. Drug Metab Rev. 2000;32:81-118.

Hewitt NJ, Lechón MJ, Houston JB, Hallifax D, Brown HS, Maurel P, et al. Primary hepatocytes: current understanding of the regulation of metabolic enzymes and transporter proteins, and pharmaceutical practice for the use of hepatocytes in metabolism, enzyme induction, transporter, clearance, and hepatotoxicity studies. Drug Metab Rev. 2007;39:159-234.

Hoehme S, Hengstler JG, Brulport M, Schäfer M, Bauer A, Gebhardt R, et al. Mathematical modelling of liver regeneration after intoxication with CCl(4). Chem Biol Interact. 2007;168:74-93.

Hoehme S, Brulport M, Bauer A, Bedawy E, Schormann W, Hermes M, et al. Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration. Proc Natl Acad Sci U S A. 2010;107:10371-6. doi: 10.1073/pnas.0909374107.

Kietzmann T. Liver zonation in health and disease: Hypoxia and hypoxia-inducible transcription factors as concert masters. Int J Mol Sci. 2019;20:E2347. doi: 10.3390/ijms20092347.

Leist M, Ghallab A, Graepel R, Marchan R, Hassan R, Bennekou SH, et al. Adverse outcome pathways: opportunities, limitations and open questions. Arch Toxicol. 2017;91:3477-505. doi: 10.1007/s00204-017-2045-3.

Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69:718-35. doi: 10.1016/j.jhep.2018.05.011.

Saito K, Negishi M, James Squires E. Sexual dimorphisms in zonal gene expression in mouse liver. Biochem Biophys Res Commun. 2013;436:730-5. doi: 10.1016/j.bbrc.2013.06.025.

Schenk A, Ghallab A, Hofmann U, Hassan R, Schwarz M, Schuppert A, et al. Physiologically-based modelling in mice suggests an aggravated loss of clearance capacity after toxic liver damage. Sci Rep. 2017;7:6224. doi: 10.1038/s41598-017-04574-z.

Schliess F, Hoehme S, Henkel SG, Ghallab A, Driesch D, Böttger J, et al. Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration. Hepatology. 2014;60:2040-51. doi: 10.1002/hep.27136.

Sezgin S, Hassan R, Zühlke S, Kuepfer L, Hengstler JG, Spiteller M, et al. Spatio-temporal visualization of the distribution of acetaminophen as well as its metabolites and adducts in mouse livers by MALDI MSI. Arch Toxicol. 2018;92:2963-77. doi: 10.1007/s00204-018-2271-3. Epub 2018 Jul 23.

Weiskirchen R, Tacke F. Liver fibrosis: Which mechanisms matter? Clin Liver Dis (Hoboken). 2016;8:94-9. doi: 10.1002/cld.581. eCollection 2016 Oct.