

Letter to the editor:

**CONCOMITANT INFLAMMATION/METABOLISM
TRANSCRIPTIONAL REGULATORY NETWORKS
IN LIVER DISEASE**

Tahany Abbas¹, Walaa Murad¹, Reham Hassan^{2*}

¹ Histology Department, Faculty of Medicine, South Valley University, Qena 83523, Egypt

² Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, South Valley University, Qena 83523, Egypt

* **Corresponding author:** Reham Hassan, Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine, South Valley University, Qena 83523, Egypt,
E-mail: reham_hassan@vet.svu.edu.eg

<http://dx.doi.org/10.17179/excli2020-1056>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>).

Dear Editor,

Recently, Campos and colleagues published a comprehensive study about transcriptional regulatory networks in liver disease (Campos et al., 2020). The authors performed a comprehensive genome-wide study including data of mouse liver tissue at eight time periods after acute CCl₄ injury. Moreover, acute damage after lipopolysaccharide as well as tunicamycin exposure were studied and the translational relevance was examined by comparing the findings to expression changes in human liver disease (Campos et al., 2020). A key observation made in all mouse and human liver diseases was the concomitant regulation of inflammatory and metabolic genes, where inflammation-associated factors are up and metabolism-associated genes down-regulated. Importantly, the same upstream regulators are involved in this response so that increased inflammation and suppressed metabolism occur within one intertwined regulatory network (Campos et al., 2020).

Upon severe damage, the liver is able to regenerate more than 70 % of its mass (Godoy et al., 2013). However, this regenerative process represents a major challenge that requires architectural reorganization (Hoehme et al., 2010; Schliess et al., 2014; Vartak et al., 2016) as well as the activation of massive transcriptional programs (Godoy et al., 2016; Zellmer et al., 2010; Ghallab et al., 2019; Grinberg et al., 2014; Leist et al., 2017). Inflammation is known to support tissue repair by elimination of the causes of injury (Karin and Clevers, 2016; Campos et al., 2014) and a link between inflammatory and regenerative responses has already been described (Michalopoulos, 2013; Hwang et al., 2019; Fortier et al., 2019). The relevance of suppressing mature liver functions, such as metabolism during inflammation, is not yet understood but a possibility is that this response helps to focus more cellular resources on regeneration. It will be interesting to learn in future if the inflammation-associated suppression of mature organ functions occurs only in liver or represents a general feature of tissue regeneration.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

- Campos G, Schmidt-Heck W, Ghallab A, Rochlitz K, Putter L, Medinas DB, et al. The transcription factor CHOP, a central component of the transcriptional regulatory network induced upon CCl4 intoxication in mouse liver, is not a critical mediator of hepatotoxicity. *Arch Toxicol.* 2014;88:1267-80. doi: 10.1007/s00204-014-1240-8.
- Campos G, Schmidt-Heck W, De Smedt J, Widera A, Ghallab A, Pütter L, et al. Inflammation-associated suppression of metabolic gene networks in acute and chronic liver disease. *Arch Toxicol.* 2020 Jan 9. doi: 10.1007/s00204-019-02630-3. [Epub ahead of print].
- Fortier M, Cadoux M, Boussetta N, Pham S, Donné R, Couty JP, et al. Hepatospecific ablation of p38 α MAPK governs liver regeneration through modulation of inflammatory response to CCl4-induced acute injury. *Sci Rep.* 2019;9:14614. doi: 10.1038/s41598-019-51175-z.
- 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.
- Godoy P, Widera A, Schmidt-Heck W, Campos G, Meyer C, Cadenas C, et al. Gene network activity in cultivated primary hepatocytes is highly similar to diseased mammalian liver tissue. *Arch Toxicol.* 2016;90:2513-29. doi: 10.1007/s00204-016-1761-4.
- Grinberg M, Stöber RM, Edlund K, Rempel E, Godoy P, Reif R, et al. Toxicogenomics directory of chemically exposed human hepatocytes. *Arch Toxicol.* 2014;88:2261-87. doi: 10.1007/s00204-014-1400-x.
- Hoehme S, Brulport M, Bauer A, Bedawy E, Schorrmann 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.
- Hwang SM, Chung G, Kim YH, Park CK. The role of maresins in inflammatory pain: Function of macrophages in wound regeneration. *Int J Mol Sci.* 2019;20:E5849. doi: 10.3390/ijms20235849.
- Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. *Nature.* 2016;529:307-15. doi: 10.1038/nature17039.
- 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.
- Michalopoulos GK. Principles of liver regeneration and growth homeostasis. *Compr Physiol.* 2013;3:485-513. doi: 10.1002/cphy.c120014.
- 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.
- Vartak N, Damle-Vartak A, Richter B, Dirsch O, Dahmen U, Hammad S, et al. Cholestasis-induced adaptive remodeling of interlobular bile ducts. *Hepatology.* 2016;63:951-64. doi: 10.1002/hep.28373.
- Zellmer S, Schmidt-Heck W, Godoy P, Weng H, Meyer C, Lehmann T, et al. Transcription factors ETF, E2F, and SP-1 are involved in cytokine-independent proliferation of murine hepatocytes. *Hepatology.* 2010;52:2127-36. doi: 10.1002/hep.23930.