Professor Norbert Hüser: the function of immune cells for liver regeneration after partial hepatectomy

Submitted Jun 05, 2013. Accepted for publication Jun 10, 2013.
doi: 10.3978/j.issn.2304-3881.2013.08.01
Scan to your mobile device or view this article at: http://www.thehbsn.org/article/view/2462/4200

Norbert Hüser (Figure 1) is working at the Department of Surgery, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany. His special clinical interests and scientific emphasis focus on hepato-pancreato-biliary surgery, transplantation and microsurgery. With many years of surgical experience and scientific work in the Munich Hepato-Pancreato-Biliary Group of the Pancreatic Center at the Klinikum rechts der Isar he gains his experience in this field.

Figure 1 Professor Norbert Hüser.

HBSN: We noticed that you have already had quite a few publications and citations so far. Could you please give a brief introduction about the current status of liver regeneration?

Prof. Hüser: Almost all clinically established resection techniques for the liver are based on its unique capability of regeneration; They stretch as far as innovative techniques of partial liver transplantation. The extremely complex and laborious operation requires both, the donor's and the recipient's liver to grow back to its original size. The surgical therapy of malignant liver tumours also makes use of the liver's extraordinary capability for tissue regeneration. The extent of resection and with that the radicalness of the operation is, however, limited by the post-operative functionality of the remaining liver. A reduction below a certain volume can lead to a life-threatening dysfunction of the remaining liver. Therefore, it is of high clinical interest to understand the regenerative and functional characteristics of the liver past surgical resection per se and in the context of a malfunction of the organism respectively. Usually liver cells demonstrate mitotic inactive characteristics due to their differentiated and highly specialised nature, they can, however, through the damaging or partial removal of the liver, re-enter into the cell cycle. This enables the liver to grow back to its original volume. The liver regeneration on a cellular and molecular level has been intensively analysed. Currently we believe that emitted cytokines and growth factors as well as other external influences trigger the activation of cascades of signal transduction with consecutive proliferation of the hepatocytes. This process is based on the interaction of several types of cells.

HBSN: You and your colleagues have made great contributions in studying liver regeneration. What do you think is the cutting-edge frontier in this area?

Prof. Hüser: The phenomenon of liver regeneration is particularly interesting for me as a surgeon. However, it still proves to be a challenge to determine which patient could benefit from a surgical therapy. Current research aims at a targeted modulation of the required processes and with that a faster initiation of regeneration after an executed resection. In particular, patients with a steatotic or cirrhotic liver could be operated at a lower morbidity.

Our goal is to identify the cells of the adaptive and innate

immune system that contribute to the liver regeneration as well as their functionalities on a molecular level. Intrahepatic leucocytes represent up to 25% of all liver cells, including the macrophages (kupffer cells), NK cells, NKT cells, CD4- and CD8-T-cells. Ultrastructural studies have proven the direct interaction between leucocytes and hepatocytes. The regeneration processes occur, dependent on the degree of liver damage, within more or less significant inflammatory reactions, including the secretion of pro-inflammatory cytokines. However, we can ascertain that at the moment only descriptive snap-shots of a possible function of immune cells in liver regeneration are known. These findings don't allow for a conclusion on the exact emergence and therefore no causality of specific interactions can be depicted.

HBSN: What's your insight about how the new development of your research can be finally applied to the clinic research and help our patients? Or it is still difficult or too far to say so? Have you ever tried to do so?

Prof. Hüser: It is essential to gain a better understanding of the molecular mechanisms supporting the liver regeneration in order to extend existing or develop new therapy approaches after an operative resection of large parts of the liver. Studies of liver regeneration in animals have grown our understanding for these processes for many decades. The complex interactions between parenchyma and non-parenchyma cells cannot be reproduced in vitro. Particularly the impact of the immune system on the process of liver regeneration can only be described in this context whilst many other factors contribute as well. For example, the increased portal pressure after a liver resection and the higher concentration of oxygen radicals after ischemia and reperfusion with consecutive, oxidative stress in the hepatocytes seem to play a certain role as well. The experimental animal model represents an ideal compromise between clinical reality and the required experimental reproducibility of these complex processes. Yet, the transferability of the results from these models into humans is limited due to the fact that we are working with artificial models. Certainly they allow conclusions for the native situation but can't represent it in its entirety Altogether we are still facing many open questions that can most likely only be answered by conducting additional studies with combined resection and knockout models. Their transfer into clinical applications will, if at all feasible, still require a lot of time.

HBSN: What can be expected in the future development of liver regeneration from where we are standing?

Prof. Hüser: In case of an uninterrupted regeneration, the human liver reaches almost its original volume again through hypertrophic and hyperplastic processes. A targeted influence on the liver regeneration on a molecular and cellular level allows the theoretic opportunity to potentially improve the clinical development through the activation of pro-regenerative transcription factors or by giving appropriate cytokines and growth factors. Such a scenario also seems possible for the living donor liver transplantation; on the one hand, complications could be reduced, on the other hand, adding cytokines or growth factors to both, the donor and the recipient, could avoid the problem of the so called "small-for-size syndrome". Recent experiments with mesenchymal stem cells have shown an improvement of liver regeneration in mouse models after a 70% hepatectomy.

The praxis offers interesting surgical approaches to inducing liver regeneration, for example a method applying two operations to prepare for an extended liver resection. During the first operation, a ligature of the right portal vein and an in situ splitting of the liver parenchyma are being performed followed by a speedy hypertrophy of the functional liver tissue. A second operation shortly after completes the resection. This technique demonstrates very well the practical usage of regenerative studies in particular for surgeons.

HBSN: I have noticed you were one of the co-authors of the article entitled "The influence of retrograde reperfusion on the ischemia-/reperfusion injury after liver transplantation in the rat", and the article said that the study observed that the lowest number of necrosis here but without the proof of significance. So could explain the reason?

Prof. Hüser: The ischemia/reperfusion injury after liver transplantation is a serious clinical problem. For this reason we evaluated the impact of different kinds of reperfusion in an animal model. As parameters for liver damage we chose serum transaminases and GLDH that also serve as liver damage markers in clinical routine. Furthermore, we analysed histology of the liver after certain time points. Interestingly, besides a reduced increase of transaminases we could also identify less necrotic areas after retrograde perfusion of the liver. In our opinion, the reason for this is the microcirculatory disturbances due to injury/reperfusion

injury. Nevertheless, this effect has to be investigated in further clinical trials.

HBSN: Thank you very much!

Cite this article as: He VJ. Professor Norbert Hüser: the function of immune cells for liver regeneration after partial hepatectomy. Hepatobiliary Surg Nutr 2014;3(1):52-54. doi: 10.3978/j.issn.2304-3881.2013.08.01

Acknowledgements

Disclosure: The author declares no conflict of interest.

(Science Editor: Vicky J. He, HBSN, editor@thehbsn.org)

