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Bridging the Gap Between Metabolic Liver Processes and Functional Tissue Structure by Integrated Spatiotemporal Modeling Applied to Hepatic Ammonia Detoxification

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The liver plays a central role in the body's overall metabolism, clearance of harmful metabolic byproducts, and detoxification of xenobiotics. The hepatic parenchyma is organized in repetitive functional units, the liver lobules, each of which is made up of hepatocytes and other nonparenchymal types of cells such as stellate cells, sinusoidal endothelial cells, and Kupffer cells. Blood enters a lobule by way of branches of the hepatic portal vein and the hepatic artery that are parts of the portal triad, then passing the liver lobule through small capillary microvessels, the liver sinusoids, while exchanging nutrients and other compounds with the lobule's cells, finally leaving the lobule by way of its pericentral vein. Hepatocytes display considerable functional differences depending on their position along the porto-central axis of the liver lobule. Hepatocytes in the upstream periportal zone differ from those in the downstream pericentral zone. This functional zonation of hepatocytes significantly affects their function in glucose and energy metabolism, xenobiotic detoxification metabolism, and hepatic ammonia detoxification.[1] Hence, lobular zonation has a significant influence on liver function and damage to the liver's metabolic zonation can lead to severe diseases. This urges the need not only for a detailed understanding of the individual processes taking place in a single cell, but for an integrated understanding of cellular, e.g., metabolic, processes and their interplay within the tissue structure.

Ammonia, as a byproduct of amino acid and nitrogen metabolism, is neurotoxic and an elevated concentration of ammonia due to liver disease is a cause for pathogenesis of hepatic encephalopathy.[2,3] Consumption of ammonia by hepatic urea production and glutamine (Gln) synthesis are critical for keeping the organisms' ammonia levels low. Hepatic Gln catabolism and synthesis are separated by zonation (Fig. 1).[4] Periportal hepatocytes express glutaminase, the enzyme that is catalyzing the hydrolysis of Gln into ammonia and glutamate. Both ammonia from Gln deamidation as well as most of the free ammonia from the blood are converted by periportal hepatocytes into carbamoylphosphate that enters the urea cycle leading to hepatic urea production. A minor part of ammonia is consumed downstream for Gln production by glutamine synthetase that is exclusively expressed in pericentral hepatocytes. A more detailed understanding of this spatiotemporal ammonia detoxification process demands an appropriate computer model to help appreciate hepatic healthy function and its deregulation upon liver disease at the tissue- and organ-level.[5]

Over the past decade, mathematical modeling has significantly influenced and driven systems-level research in biology and medicine.[6] Detailed mathematical models have been developed describing biological systems at multiple levels, including metabolic[7] and gene-regulatory networks,[8] signal transduction pathways, like insulin signaling,[9] or physiological models on the organ-level, such as the cardiac physiome.[10] In particular, large models of the cellular metabolism were constructed,[11,12] also with a particular emphasis on liver-specific processes.[13]

Despite the enormous advances in modeling and simulation of biological systems, the multiscale character of these systems still presents significant conceptual and computational challenges.[14] Multiscale modeling is an emerging field aiming at a mechanistic understanding of biological interaction networks at the

Abbreviations: Cbm-P, carbamoylphosphate; Gln, glutamine; GLNase, glutaminase; Glu, glutamate; GS, glutamine synthetase.

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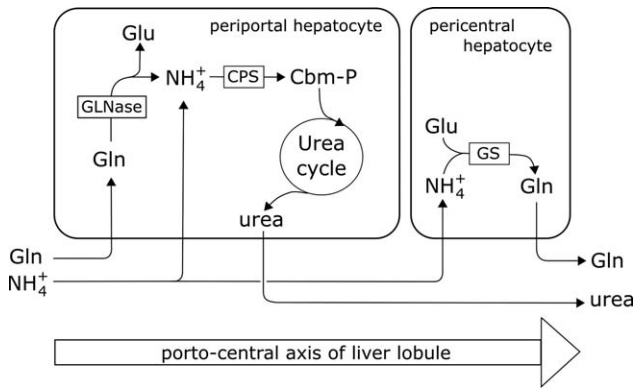

Fig. 1. Zonation of hepatic ammonia detoxification. In the intact liver, blood enters the liver lobule by way of its sinusoids, passing first periportal and later pericentral hepatocytes. In the periportal hepatocytes, glutamine (Gln) and ammonia from the blood are converted into urea. Gln is hydrolyzed by glutaminase (GLNase) into glutamte and ammonia. Ammonia is subsequently converted into carbamoylphosphate (Cbm-P) by way of carbamoyl phosphate synthetase (CPS) and urea by way of the urea cycle. Ammonia escaping the periportal urea production is used by pericentral hepatocytes for resynthesis of Gln from ammonia and glutamate (Glu) catalyzed by glutamine synthetase (GS) (modified after Schliess et al.[15]).

subcellular, cellular, intercellular, tissue, and organismic level. Major challenges exist in the development of predictive models that span the gap between molecular processes at the cellular level and comprehensive models at the organismic level that allow *in silico* simulation studies and analysis. This urges the need for integrative modeling frameworks that leverage advances in the spatiotemporal computational study of fundamental human physiological processes to advance understanding of these processes on all those levels of complexity that are required and sufficient to understand major systems properties

In this issue of HEPATOLOGY, Schliess et al.[15] apply the concept of integrated spatiotemporal modeling to hepatic ammonia detoxification to study the effect of liver damage and regeneration on this particular metabolic function. Therefore, they make use of a previously published spatiotemporal computer model of hepatic lobular regeneration that assumes some principles of cellular interaction needed to establish a functional tissue microarchitecture, such as the alignment of proliferating hepatocytes along the lobular sinusoids during liver regeneration.[16] This model allows the simulation of the destruction and regeneration of a liver lobule after carbon tetrachloride (CCl_4) administration, but not the simulation of spatiotemporal metabolic processes such as ammonia detoxification. In this issue of HEPATOLOGY, Schliess et al. use data from mouse liver perfusion experiments with different concentrations of ammonia and Gln from both intact and impaired tissue. By monitoring effluent concentrations of ammonia, Gln, and urea they were able to build a metabolic model that takes into account the zonation of the process, i.e., a two-compartment model reflecting the periportal and pericentral zone, respectively. By joining both the spatiotemporal model and the metabolic zonation model, they were able to build an integrated metabolic spatiotemporal model that was subsequently used to study the hepatic turnover of ammonia, Gln, and urea.

The integrated model was extended to a group of seven lobuli and allows the time-dependent prediction of the volume of hepatocytes in the periportal and pericentral compartment, respectively. Furthermore, simulation results on ammonia urea and Gln concentrations for each individual cell were used for an animation of the spatiotemporal processes during liver damage and regeneration. The visualization shows in detail the temporal formation of necrosis of the pericentral lobular region due to CCl_4 administration and the hepatic regeneration completed 6 days after intoxication. Schliess et al. demonstrate that the integrated metabolic spatiotemporal model can reproduce observed data from perfusion experiments: Increasing ammonia concentrations give rise to increasing ammonia release that was significantly elevated due to the toxic effect of CCl_4 on the pericentral hepatocytes correlating with almost no Gln production, whereas periportal urea production remained largely unaffected by CCl_4 treatment. These results show the important interplay on the cellular and intercellular level that is needed for correct metabolic liver function and how this process is affected during damage and regeneration. The study is complemented by a simplified model of blood circulation taking into account skeletal muscles, kidney, and brain as three further ammonia detoxifying organs as well as the gastrointestinal tract. Analysis of this model demonstrates an increased extrahepatic ammonia detoxification and implicates alterations in amino acid metabolism during regeneration after CCl_4 intoxication.

Taken together, this important work expands our understanding of the effect of pericentral liver damage due to toxic substances or liver disease, as well as of major metabolic functions, in particular ammonia detoxification and Gln metabolism. The work by Schliess et al. is a first step in integrated spatiotemporal modeling bridging the layers of cellular metabolic functions and intercellular processes towards an improved understanding of liver function. This work highlights the importance of multiscale modeling

towards a virtual physiological organism for systems-based understanding.

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