Highlight report: physiologically-based modeling of diseased liver tissue

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Received: 22 November 2017 / Accepted: 23 November 2017 / Published online: 25 November 2017
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Recently, Arne Schenk et al. have published an interesting study to understand the relationship between the fraction of damaged liver tissue and loss of metabolic function (Schenk et al. 2017). Acute intoxication of the liver, for example, by carbon tetrachloride or paracetamol leads to destruction of a fraction of the hepatocytes (Godoy 2011). The fraction of destroyed hepatocytes can be quantified by immunostaining or more elaborate imaging techniques (Hoehme et al. 2010; Hammad et al. 2014; Ghallab et al. 2016). It can be expected that reduction of the number of hepatocytes leads to reduced metabolism of drugs and consequently increased half-life. In principle, three scenarios are possible: (1) the loss of tissue is directly proportional to the decrease of metabolic capacity, e.g., destruction of 30% of the hepatocytes decreases the amount of metabolites formed by 30%; (2) loss of metabolic capacity is less compared to the fraction of lost hepatocytes. This would indicate that the surviving hepatocytes up-regulate their metabolic performance to compensate for the loss; (3) the loss of metabolic capacity goes beyond the mere loss of hepatocytes. Interestingly, this third scenario was observed by the authors and was named ‘aggravated loss’. A probable explanation is that either the surviving hepatocytes express less metabolizing enzymes compared to healthy livers or the destroyed microarchitecture compromises function.

In recent years, much progress has been achieved in PBPK modeling (Kuepfer et al. 2016; Thiel et al. 2015; Jones et al. 2009; Meyer et al. 2012). Moreover, techniques of spatio-temporal tissue modeling have been established that allow simulations of how specific biological processes contribute to liver function (Hoehme et al. 2017; Friebe et al. 2015; Drasdo et al. 2014a, b; Schliess et al. 2014;

Vartak et al. 2016). Such techniques allow the *in silico* analysis of which degree of loss of tissue causes loss of function (or metabolic capacity) under the assumption of a proportional relationship. As always, the model prediction has to be compared to the experimental data. For this purpose, Schenk et al. (2017) time-dependently analyzed the concentrations of a set of drugs (midazolam, torsemide, codein, talinolol, pravastatin and caffeine) in the portal vein and liver vein of mice and compared the situation in healthy mice and after CCl₄ intoxication. The mechanisms of hepatotoxicity and their functional consequences are currently an intensively studied field of research (Kyriakides et al. 2016; Ghallab 2015; Mazzanti et al. 2015; Tolosa et al. 2015; Stöber 2016; Stoeber 2015a, b; Hammad 2013; El-Zawahry et al. 2016). The modeling techniques presented by Schenk et al. may certainly help to better understand the relationship between structural loss of tissue and its consequences on the function.

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