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Guest editorial:

PATHOPHYSIOLOGY OF CHOLESTATIC LIVER DISEASE AND ITS RELEVANCE FOR IN VITRO TESTS OF HEPATOTOXICITY

Regina Stöber

Leibniz Research Centre for Working Environment and Human Factors at TU Dortmund (IfADo), Ardeystrasse 67, 44139 Dortmund, Germany; e-mail: stoeber@ifado.de

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Recently, Peter Jansen from the Department of Gastroenterology and Hepatology and colleagues published a comprehensive review about the mechanisms leading to cholestatic liver disease (Jansen et al., 2016). The authors describe the morphological changes at different topological domains of the biliary tree: while large bile ducts respond by enlargement of ductular diameter to maximize their volume, intralobular bile ducts respond by branching and surface corrugation to optimize their capacity to reabsorb bile salts (Vartak et al., 2016). A key mechanism in cholestatic liver disease is that the bile canaliculi in liver lobules become leaky, and toxic bile can get into contact with parenchymal cells leading to cytotoxicity and necrosis, a phenomenon also named bile infarct.

For toxicologists the perhaps most important lesson learned from this review is that cholestatic liver disease may have an ascending and a descending pathophysiology. For example primary sclerosing cholangitis and primary biliary cholangitis begins with early lesions ‘downstream’ in bile ducts which leads to bile salt-mediated injury ‘upstream’ in liver parenchyma. In contrast, most forms of drug induced cholestasis have a descending pathophysiology, where damage of hepatocytes represents the initial key event.

Considering this classification it may be justified that in vitro systems to identify hepatotoxic compounds focus on hepatocytes (Miszczuk et al., 2015; Tolosa et al., 2015; Björnsson, 2015; Stöber, 2015a, b). Currently, large research programs focus on hepatocyte in vitro systems, either using functional assays (Godoy et al., 2013; Reif et al., 2016) or genome wide expression analysis (Schaap et al., 2015; Benet et al., 2014; Grinberg et al., 2014).

However, it should be taken into account that also toxic cholestasis may in rare cases have an ascending pathophysiology. For example, 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) primarily causes damage to bile ducts, while parenchymal damage occurs as a secondary event (Fickert et al., 2007).

Therefore, insufficient sensitivity in currently performed in vitro screens for hepatotoxicity may be a consequence of neglecting compounds acting by an ascending pathophysiology, where cholangiocytes and not hepatocytes represent primary targets.

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