Archives of Toxicology (2019) 93:2709–2710
https://doi.org/10.1007/s00204-019-02535-1

EDITORIAL

Highlight report: caspase 8 as a therapeutic target in chronic liver disease

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Received: 8 August 2019 / Accepted: 12 August 2019 / Published online: 17 August 2019

Apoptosis can be induced by extrinsic death receptor-mediated pathways (Yuan 1997; Reed 2000; Chaudhary et al. 2013) where caspase 8 acts as downstream executioner of cell death (Alnemri et al. 1996; Li et al. 2010; Desbarats and Newell 2000; Yuan 1997). In the past years, mouse models with inducible and cell type-specific deletion of caspase 8 have been established to understand how caspase 8 contributes to chronic liver disease (Chaudhary et al. 2013; Liedtke et al. 2011). The ubiquitous knockout of caspase 8 led to enhanced liver injury in mouse models of cholestatic liver damage as evidenced by a strong increase in transaminases and bilirubin as well as increased fibrosis compared to wild-type controls (Chaudhary et al. 2013). This has been explained by inhibition of apoptosis in immune cells, leading to stronger infiltration of mononuclear cells into the liver tissue and to immune cell-mediated liver damage. However, a recent landmark publication demonstrated that cell type-specific deletion of caspase 8 in parenchymal cells of the liver protects against obstructive cholestasis induced by ligation of the common bile duct (Cubero et al. 2018). The knockout of caspase 8 in cholangiocytes decreased necrotic foci and ductular reaction (Cubero et al. 2018). Therefore, caspase 8 is a promising therapeutic target in obstructive cholestasis but strategies have to be identified to inhibit caspase 8 in cholangiocytes without influencing immune cells, because inhibition in immune cells may lead to immune-mediated hepatotoxicity (Cubero et al. 2018).

Currently, mechanisms of liver damage and regeneration as well as the pathophysiology of cholestasis represent a very active field of research (Rodrigues et al. 2018; Svinka et al. 2017; Leist et al. 2017; Hoehme et al. 2010; Ghallab et al. 2016). It has been shown that cholestatic liver disease usually evolves over time with an ascending course of the disease process with first lesions in bile ducts, followed by damage of liver parenchyma (Jansen et al. 2017). In this situation, concentrations of bile acids in the biliary tract increase, lead to ruptures of the apical and later basolateral hepatocyte membranes and thereby cause shunting of bile acids from canaliculi into the blood (Ghallab et al. 2019). At the level of interlobular bile ducts, cholestasis leads to adaptive remodeling by cholangiocyte proliferation, branching as well as looping of ducts, also known as ductular reaction (Vartak et al. 2016). Therefore, the concept of Cubero and colleagues (2018) to reduce apoptosis specifically in cholangiocytes to delay progression of cholestatic liver disease seems to be reasonable. However, the challenge remains how the required cell type-specific inhibition of caspase 8 can be achieved in patients.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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