Arch Toxicol (2012) 86:1331–1332
DOI 10.1007/s00204-012-0921-4

EDITORIAL

Alcohol hepatotoxicity: Kupffer cells surface to the top

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Published online: 15 August 2012

In this issue of the Archives of Toxicology, Arthur I. Cederbaum from New York Mount Sinai School of Medicine gives a review on cytokine-mediated hepatotoxicity including a state-of-the-art discussion of the involved signalling pathways (An et al. 2012). A key mechanism of alcoholic liver disease is that ethanol consumption increases levels of gut-derived endotoxins to the portal circulation. As a consequence, Kupffer cells are activated through Toll-like receptors, particularly Toll-like receptor 4 (TLR-4). A well-known consequence of TLR-4-mediated activation of Kupffer cells is secretion of tumour necrosis factor alpha (TNF-α), which mediates inflammation and apoptosis. TNF-α signals through two receptors, TNF-α-R1 and TNF-α-R2, which are expressed at higher levels on the hepatocyte membranes compared to all other (non-parenchymal) liver cell types. Therefore, TNF-α is a prototypical cytokine of the Kupffer cell–hepatocyte axis. Cederbaum discusses a number of further mechanisms relevant to alcoholic liver disease, including IL-8 and IL-18, the protective role of adiponectin, AMP-activated protein kinase and transcription factors regulating lipid synthesis, such as SREBPS and sirtuin 1.

Hepatotoxicity remains a major reason for drug withdrawal from clinical use (Hewitt et al. 2007; Knobeloch et al. 2012). Therefore, a lot of energy is currently invested into development and improvement of hepatocyte in vitro systems to predict hepatotoxicity (De Kock et al. 2011; Wobus and Löser 2011; Heise et al. 2012; Zellmer et al. 2010; Godoy et al. 2009, 2010a, b; Schumann et al. 2009). However, one of the critical aspects highlighted in the article of Arthur Cederbaum is that hepatocytes may not be the primary 'sensor' of hepatotoxicity, but rather react to cytokines released from Kupffer cells. Similar constellations have been reported for other non-parenchymal liver cells, such as sinusoidal endothelial cells and stellate cells (Hoehme et al. 2010; Ding et al. 2010). One of the merits of the current review (An et al. 2012) is that it highlights the role of cell–cell communication between non-parenchymal cells and hepatocytes. The article is a must-read for anyone interested in mechanisms of hepatotoxicity.

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