Alcohol-induced liver injury: how a small molecule overwhelms one of the cell types with the best regeneration capacity of the human body

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One of the outstanding features of the liver is its enormous regeneration capacity that has evolved to protect animals from liver loss by food toxins (Michalopoulos and DeFrances 1997). The best known experimental system for the study of the regenerating liver is a simple operation in which two-thirds of the liver of a rat or mouse is removed. The residual lobes enlarge and within only 7 days make up for the mass of the removed tissue. Furthermore, after intoxication with chemicals such as CCl_4 that can kill up to 50% of the hepatocytes, regeneration also results in complete restoration of intact liver tissue (Höhme et al. 2007; Brulport et al. 2007; Aurich et al. 2007). In addition in larger animals and humans, the regeneration capacity of the liver is excellent. Another experimental system to study the liver regeneration is that of mice deficient in fumarylacetoacetate hydrolase causing a permanent deterioration of hepatocytes and finally death of the animal (review: Hengstler et al. 2005). Hepatocytes transplanted into these livers colonize and rescue the entire organ (review: Nussler et al. 2006). Hepatocytes from the rescued livers can be transplanted in second generation livers, and so forth. Using this approach of serial transplantation, it has been shown that a single hepatocyte has the clonogenic capacity to form at least 50 livers (Overturf et al. 1996). Besides its amazing regenerative capacity, the liver is characterized by its outstanding

capability to adapt to new situations. When livers from baboons were transplanted into humans, the size of the transplanted liver rapidly increased (reviewed in: Michalopoulos and DeFrances 1997). Vice versa livers from large dogs transplanted into small dogs gradually decreased in size until it reached an adequate volume to the smaller body size. It is difficult to comprehend how an organ with such an amazing regeneration and adaptation capacity can be overwhelmed by the relatively low and nontoxic ethanol concentrations resulting from drinking alcohol. Nevertheless, alcohol consumption is the major cause of liver disease in Western countries. An initial fatty acid change or steatosis, characterized by fat globules (macrovesicular steatosis) may lead to an inflammatory reaction, alcoholic hepatitis. Both, steatosis and alcoholic hepatitis may be reversible. In contrast, the late stage, cirrhosis, marked by fibrosis and compromised liver architecture is irreversible. One of the most important mechanisms causing alcoholic liver disease is the generation of oxidative stress, which is a cutting edge topic of our journal (Adam and Laufs 2008; Verstraeten et al. 2008; Bolt and Hengstler 2008; Glahn et al. 2008; Helal and Helal 2009; Beyersmann and Hartwig 2008; Arivarasu et al. 2008; Matés et al. 2008; Hengstler and Bolt 2007, 2008; Abe et al. 2008; Nishimura et al. 2008; Kolli et al. 2008; McDermott et al. 2008; Manna et al. 2008; Sivalingam et al. 2008; Schug et al. 2008; Binner et al. 2008; Dika Nguea et al. 2008). The editors are happy that Dr. Arthur I. Cederbaum, Mount Sinai School of Medicine, New York has contributed a comprehensive review about the role of oxidative stress in alcohol-induced liver injury. The authors discuss the role of Kupffer cells, lipid peroxidation, formation of the 1-hydroxyethyl radical, *S*-adenosyl-L-methionine, NO production and protein adducts. Special emphasis is placed on the role of CYP2E1 in generating reactive-oxygen species.

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